Cyramza (*ramucirumab*)

February 26, 2020

Oncologic Drug Advisory Committee
Eli Lilly and Company

Introduction

Allen Melemed, MD, MBA

Distinguished Medical Scholar and Senior Director
Global Regulatory Affairs, Oncology
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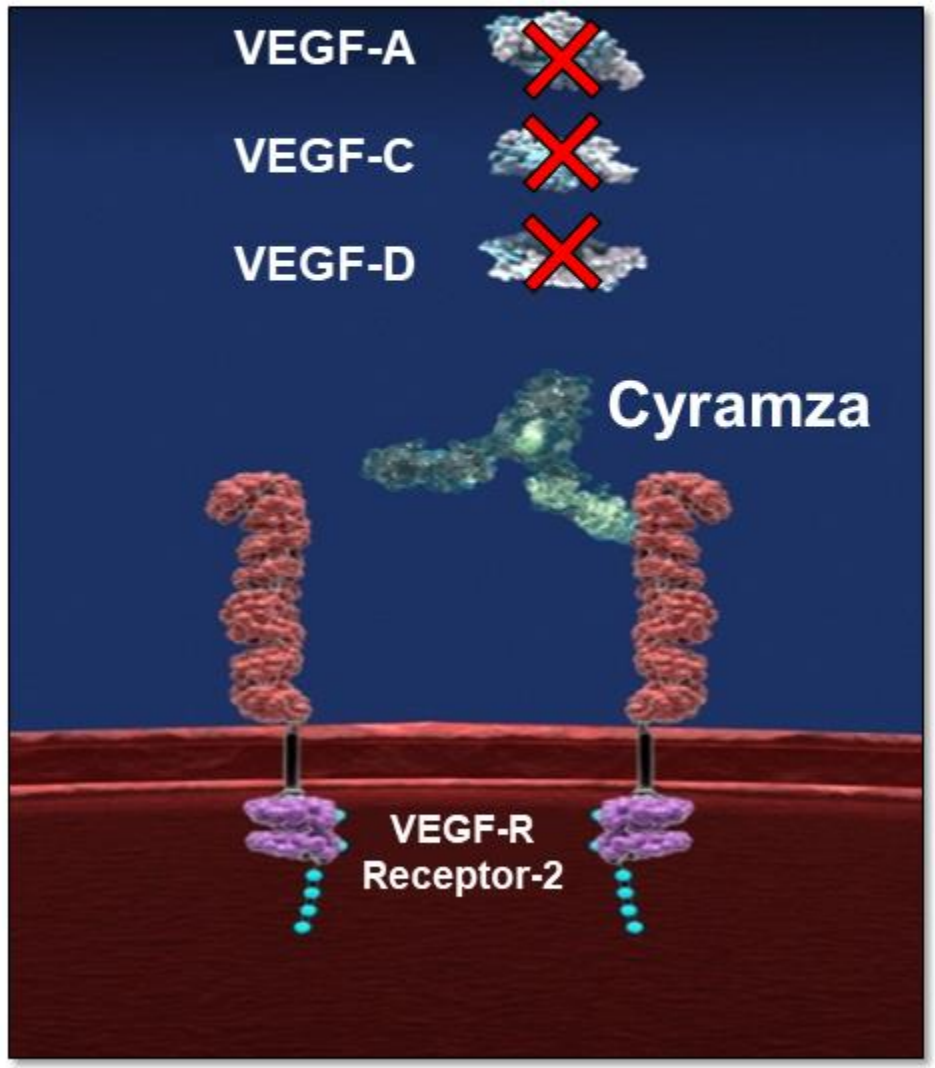
Cyramza Approved in US for More Than 5 Years

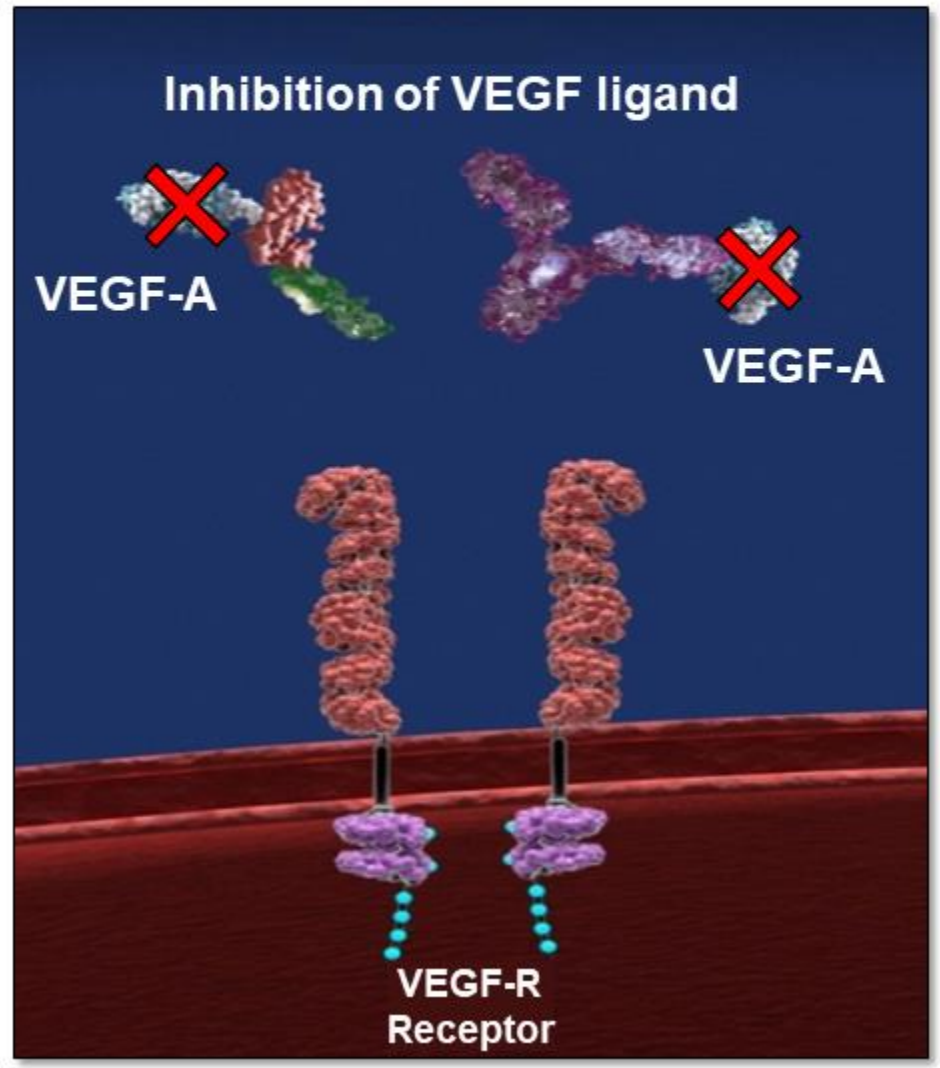
- Approved in 2014 in combination with docetaxel in 2nd line treatment of non-small cell lung cancer (NSCLC)
  - Based on REVEL study
  - Improved progression-free survival and overall survival
- Additional 2nd line indications
  - Gastric or gastroesophageal junction adenocarcinoma
  - Colorectal cancer
  - Hepatocellular carcinoma
- > 125,000 patients treated with Cyramza worldwide

Proposed New Indication

- Cyramza is indicated in combination with erlotinib for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with *activating epidermal growth factor receptor (EGFR) mutations*

Cyramza Binds Specifically to VEGF Receptor-2, Blocking VEGF-A, VEGF-C and VEGF-D



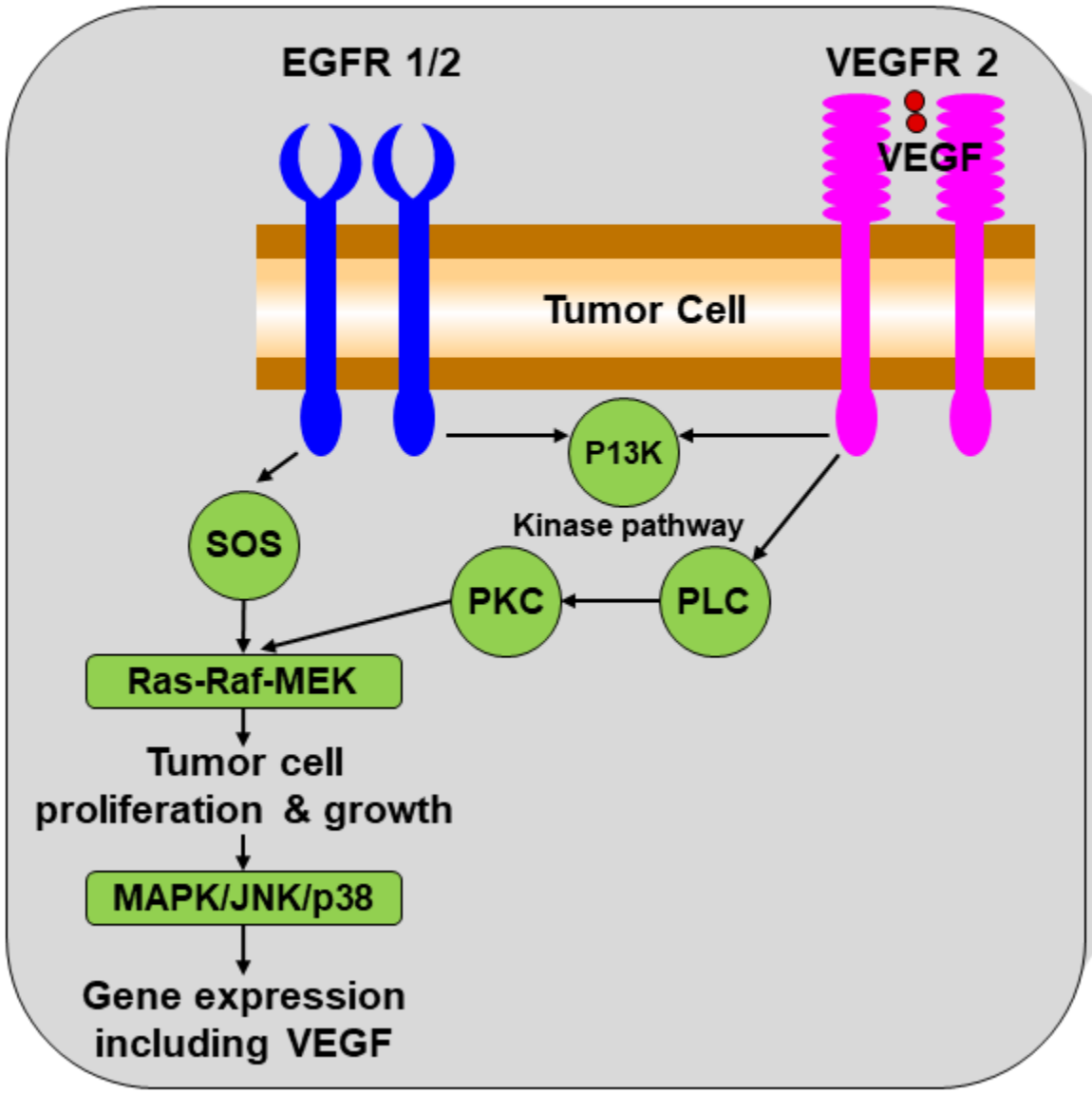


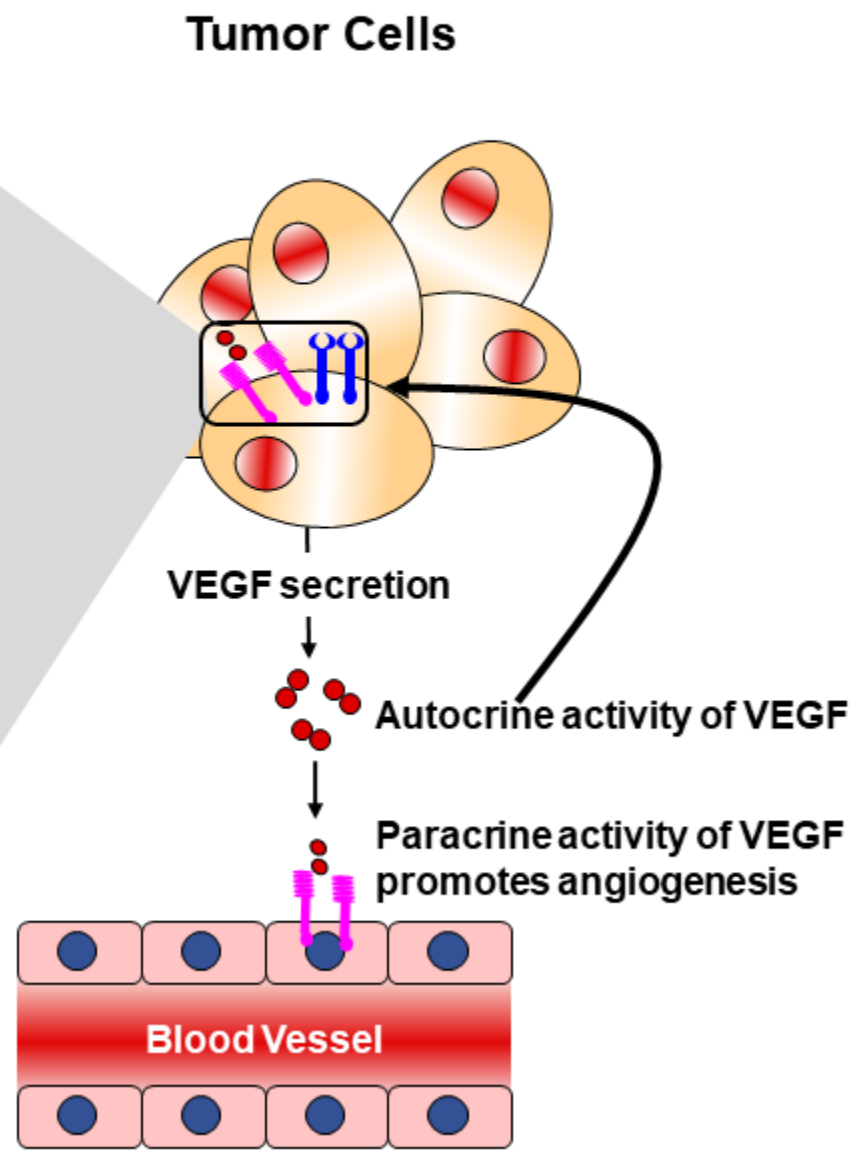
Adapted from Clarke JM and Hurwitz HI. *Expert Opin Biol Ther* 2013.

Rationale for Combination Therapy in Treatment of NSCLC with Activating EGFR Mutations

- Preclinical data suggest
  - Dual blockade of VEGF and EGFR pathways is more effective than either approach alone
- Similar to other synergistic combinations of targeted agents
  - BRAF / MEK inhibition
- One agent inhibits oncogenic driver, other inhibits target downstream of oncogenic driver

Targeting Interconnected Pathways of VEGFR and EGFR





Adapted from Sarkar and Mandal 2009

PFS Recognized as Relevant Clinically Meaningful Endpoint in EGFR-Mutated NSCLC[1-4]

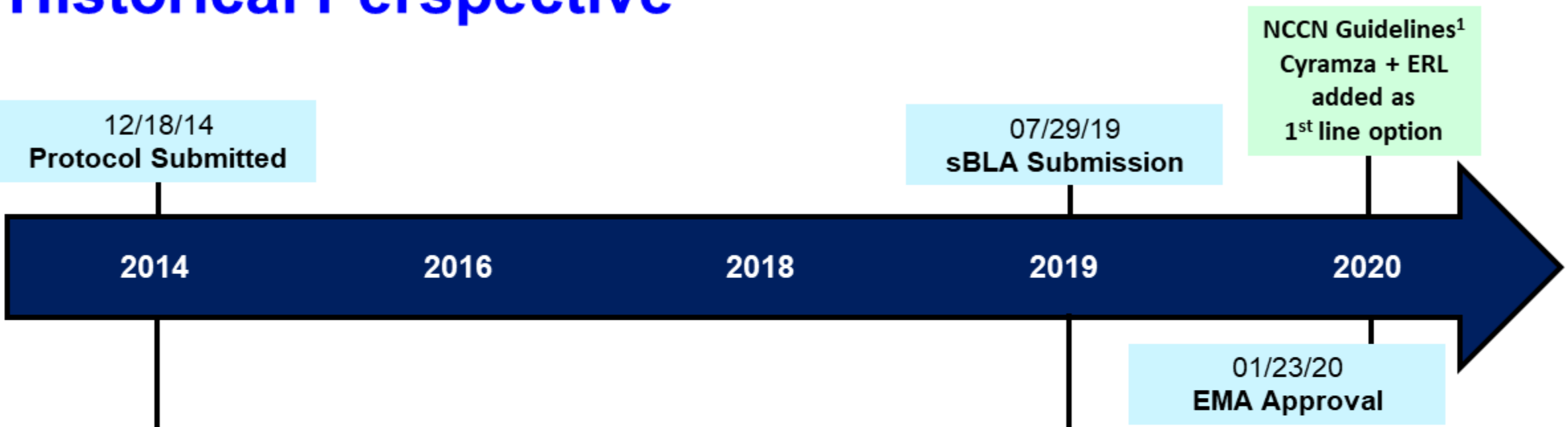
- Historically approvals for NSCLC based on significant improvement in OS, as median survival short (< 1 year)
- PFS is a relevant primary endpoint when OS is of long duration and affected by subsequent cancer therapies
- Metastatic EGFR-mutated patient population
  - OS is long, confounded by multiple lines of subsequent therapies
  - PFS is best assessment of treatment effect

1. Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry, FDA, April 2015
2. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry, FDA, December 2018
3. ASCO public workshop April 2003
4. FDA ODAC meeting December 2003

FDA Approvals as First-Line Treatments for NSCLC with Activating EGFR Mutations

	1st Generation		2nd Generation		3rd Generation
	Gefitinib vs chemo (July 2015)	Erlotinib vs chemo (May 2013)	Afatinib vs chemo (July 2013)	Dacomitinib vs gefitinib (Sept. 2018)	Osimertinib vs gef or erl (April 2018)
Median PFS (months)	Study 1: 9.7 Study 2: 10.9 vs 7.4	10.4 vs 5.2	11.1 vs 6.9	14.7 vs 9.2	18.9 vs 10.2
Magnitude of Effect on PFS (months)	Study 2: 3.5	5.2	4.2	5.5	8.7

Historical Perspective



FDA Meeting (November 2014)

Aligned: PFS would support regulatory approval

- Clinically meaningful and statistically persuasive
- Consistent effects in relevant subpopulations
- Consistent effects in key secondary endpoints
- No evidence of an OS decrement
- Acceptable risk-benefit profile

sBLA Teleconference (June 2019)

FDA stated: PFS not sufficient for regular approval

- Approval of therapies targeting oncogenic driver mutations based on PFS
- Additional safety considerations
- Recommended waiting for mature OS to file

1. Ettinger, NCCN Guidelines, 2020

RELAY Data Demonstrate Positive Benefit-Risk

- Cyramza + erlotinib demonstrated statistically and clinically significant improvements in PFS
  - 7 month difference in mPFS
  - 41% reduction in the hazard of disease progression or death
  - Consistent across subgroups and sensitivity analyses
- Supported by secondary and exploratory endpoints
- Observed toxicity well-managed
- First-line option gives oncologists a dual targeted therapeutic strategy to treat patients

Agenda

Unmet Medical Need

Everett Vokes, MD
John E. Ultmann Professor of Medicine and Radiation Oncology
Physician-in-Chief, University of Chicago Medicine and Biological Sciences Chair, Department of Medicine

Efficacy

Paolo Abada, MD, PhD
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Safety

Carla Visseren-Grul, MD
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Clinical Perspective

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David Bruton, Jr. Chair in Cancer Research

Unmet Medical Need

Everett Vokes, MD

John E. Ultmann Professor of Medicine and Radiation Oncology
Physician-in-Chief, University of Chicago Medicine and Biological Sciences Chair, Department of Medicine

Metastatic EGFR-Mutation NSCLC Epidemiology and Goal of Treatment

- 32% of NSCLC are EGFR-mutation positive[1]
  - Patients frequently present with advanced or metastatic disease at diagnosis[2]
  - Median OS ~ 25 months[3]
  - 5-year survival of ~ 14%[3]
- Treatment focused on extending life and delaying disease progression[4]

1. Yue-Lun 2016; 2. Reiss, 2013; 3. Okamoto, 2018; 4. Fallowfield, 2012

EGFR Pathway Frequent Driver in Development and Progression of NSCLC

- Activating EGFR mutations found
  - 10 – 20% of Caucasians, 40 – 60% of Asians[1]
  - Females
  - Nonsmokers
  - Adenocarcinoma histology
- Patient population with fewer comorbidities

1. Zhang, 2016

EGFR Mutation Subtypes

- Most common activating mutations being[1]
  - Deletions within exon 19
  - Substitution in exon 21 (L858R)
- Mutations associated with sensitivity to small-molecule EGFR tyrosine kinase inhibitors (TKIs)

1. Murray, 2008

Current Treatments for Advanced EGFR-Mutated NSCLC

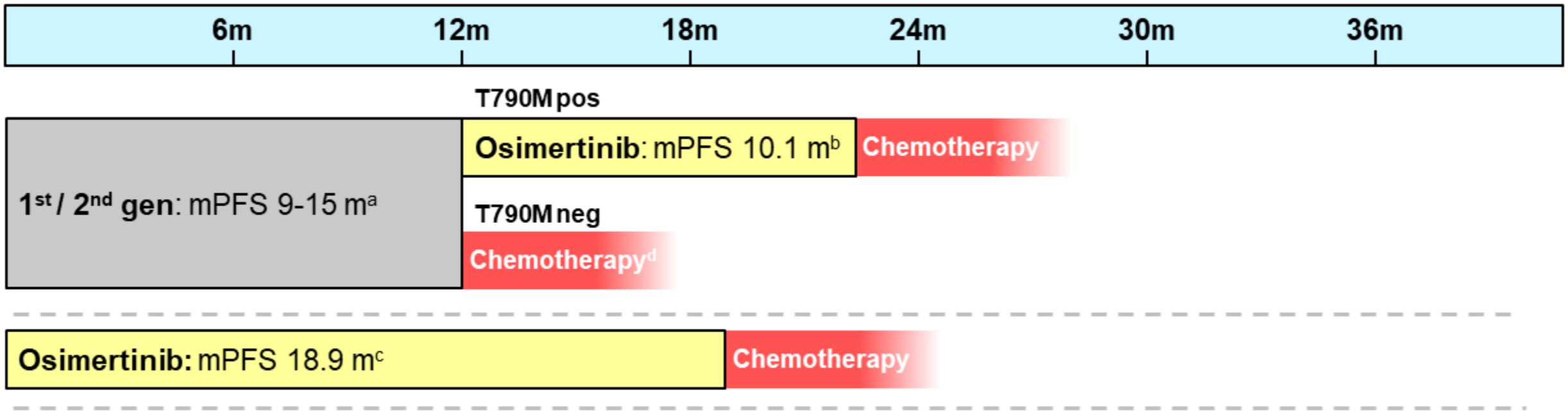
- First generation EGFR TKIs
  - Gefitinib, erlotinib
- Second generation EGFR TKIs
  - Afatinib, dacomitinib
- Third generation EGFR TKI
  - Osimertinib (approved 2017: second-line to target T790M)
  - Osimertinib (approved 2018: first-line)

Limitations of Current Monotherapy Options

- EGFR TKIs associated with treatment resistance and eventual disease progression
- Mechanisms of resistance after first-line osimertinib heterogeneous and mostly non-targetable
  - No options, other than chemotherapy, once patients progress on osimertinib
- Immunotherapy options for EGFR mutated tumors rarely successful[1]

1. Yu, 2018

Current Treatment Strategies in EGFR-Mutant NSCLC



a: Mitsudomi, 2010; Maemondo, 2010; (NEJ002); Park, 2016 (LUX-Lung 7), Wu, 2017 (ARCHER 1050), Rosell, 2012 (EURTAC), Zhou, 2011 (OPTIMAL), Furuya, 2018 (NEJ026), Sequist, 2013 (LUX Lung 3), Wu, 2014 (LUX-Lung 6); b: Mok, 2017 (AURA3); c: Soria, 2018 (FLAURA); d: Soria, 2015

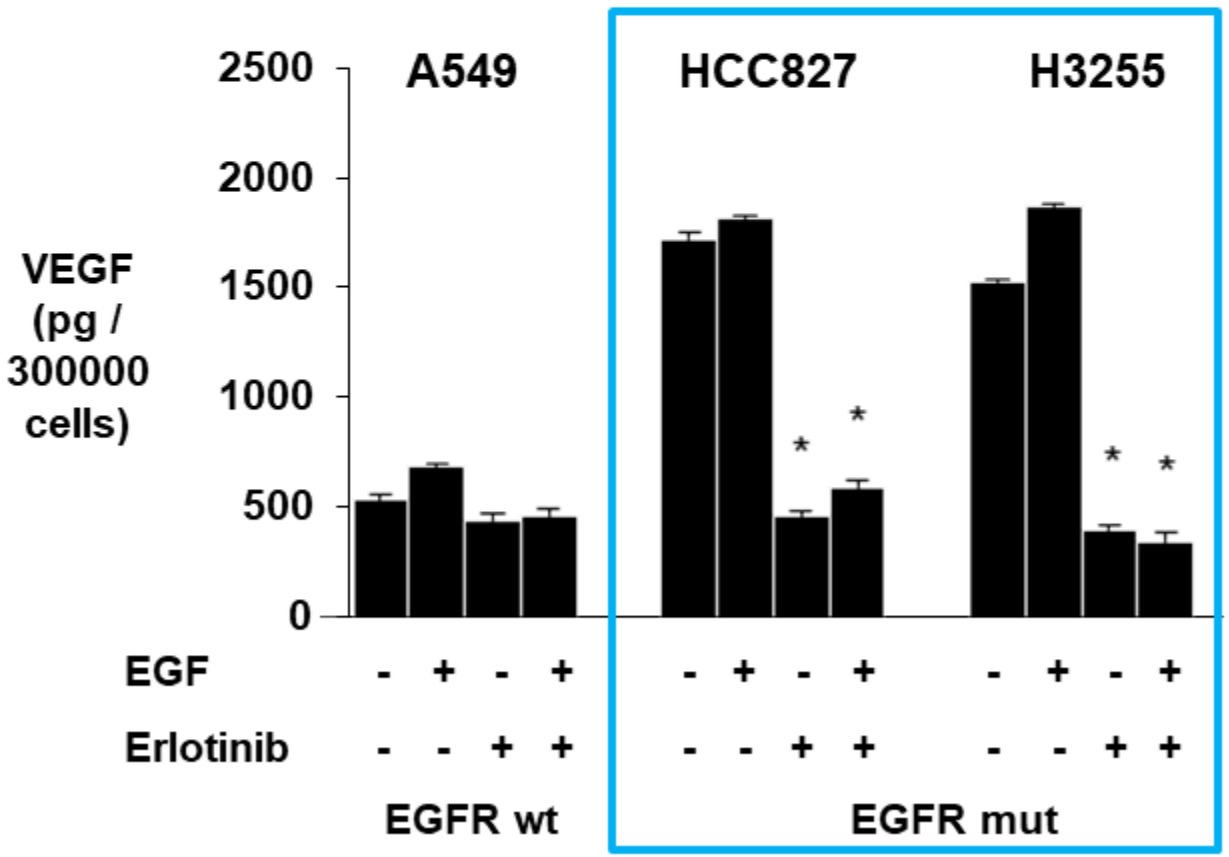
Preclinical Rationale for Combining EGFR TKIs with VEGF Pathway Inhibition

- EGFR mutant tumors more "VEGF-dependent" than EGFR wild-type tumors
- Dual VEGF / EGFR pathway blockade enhances efficacy
  - EGFR mutations result in constitutive upregulation of VEGF and HIF1α in EGFR-mutant cells
  - EGFR inhibition lowers VEGF levels, resulting in anti-angiogenic effects
  - Acquired EGFR inhibitor resistance associated with increase in VEGF

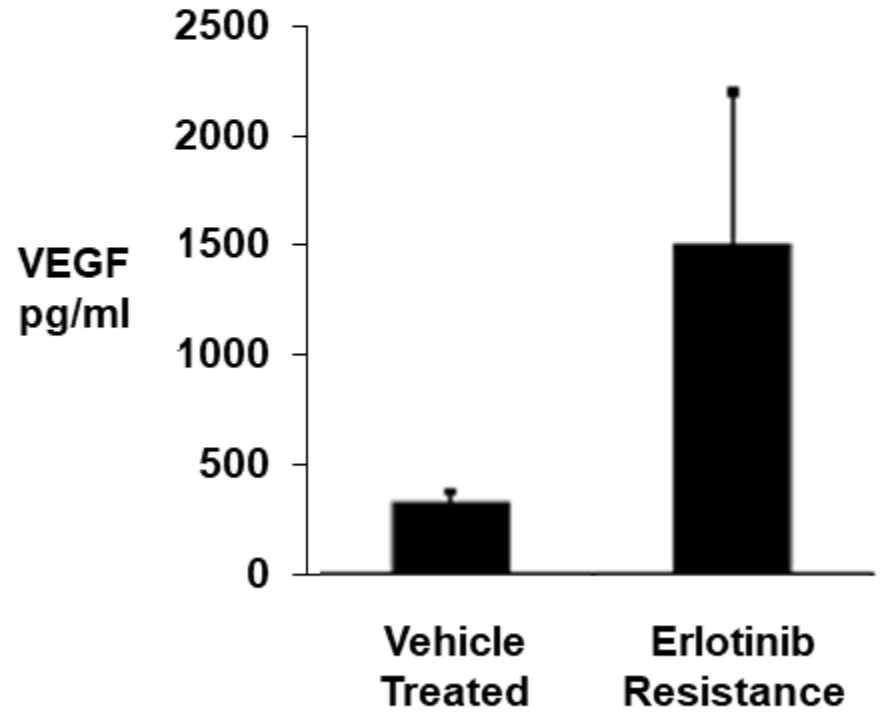
Ciardiello, 2001; Viloria-Petit, 2001; Luwor, 2005; Xu, 2010; Naumov, 2009

Strong Preclinical Rationale for VEGFR-2 + EGFR

EGFR activating mutations upregulate VEGF and HIF-1α in EGFR-mutant NSCLC cells



EGFR inhibitor resistance associated with increased plasma VEGF levels



Cascone 2008; Xu 2010; Naumov 2009.
*Statistically significant

Ongoing Need for Additional First-Line Treatment Options

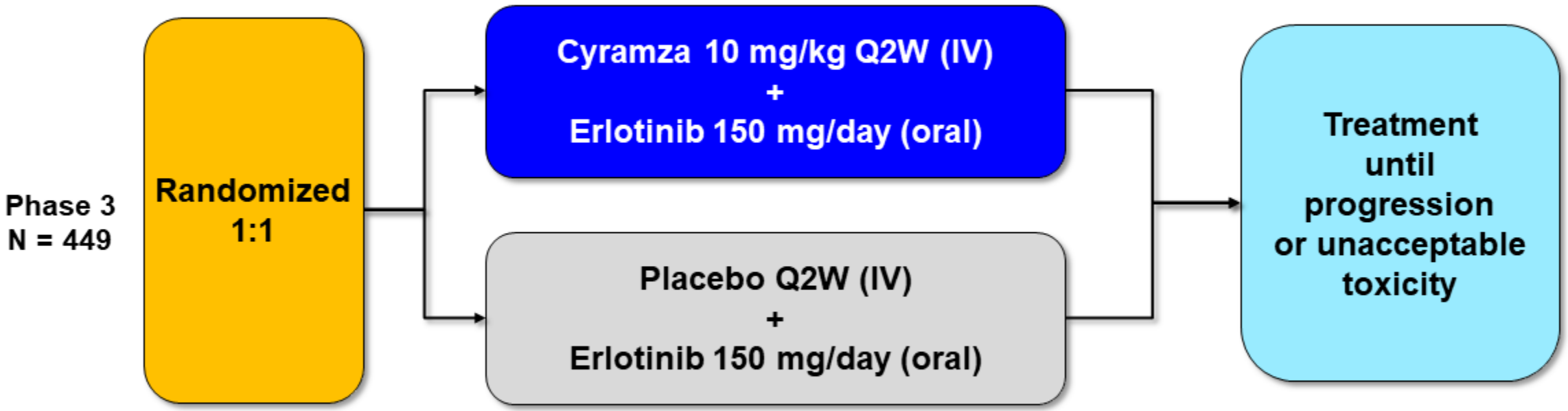
- Provide clinically meaningful benefits
  - Delaying disease progression
  - Delaying time to chemotherapy
- Expanding selection of first-line options allows oncologists greater strategic choice

Cyramza Efficacy

Paolo Abada, MD, PhD

Senior Medical Director
Cyramza Global Product Development, Oncology
Eli Lilly and Company

RELAY: Phase 3 Study Design



- Imaging (CT or MRI) at baseline, every 6 weeks through 72 weeks, then every 12 weeks
- Choice of post-progression therapy at discretion of investigator and not restricted

RELAY: Primary Endpoint – PFS

- Progression free survival (PFS)
  - Time from randomization until radiographic documentation of progression or death
  - Investigator-assessed
- Powered to show a clinically meaningful improvement of ≥ 4.5 months vs erlotinib alone

RELAY: Secondary Efficacy Endpoints

- Objective response rate (ORR)
- Disease control rate (DCR)
- Duration of response (DoR)
- Patient Reported Outcomes
- Overall survival (OS)

RELAY: Key Inclusion Criteria

- Confirmed diagnosis of Stage IV NSCLC
- Eligible for first-line treatment with erlotinib
  - Confirmed tumor with EGFR exon 19 deletion or exon 21 (L858R) substitution mutation
- ECOG performance status of 0 or 1 and adequate organ function

RELAY: Key Exclusion Criteria

- T790M EGFR mutation
- CNS metastases
- Clinically active interstitial lung disease
- Prior anticancer therapy for advanced disease

RELAY: Demographics Well-Balanced

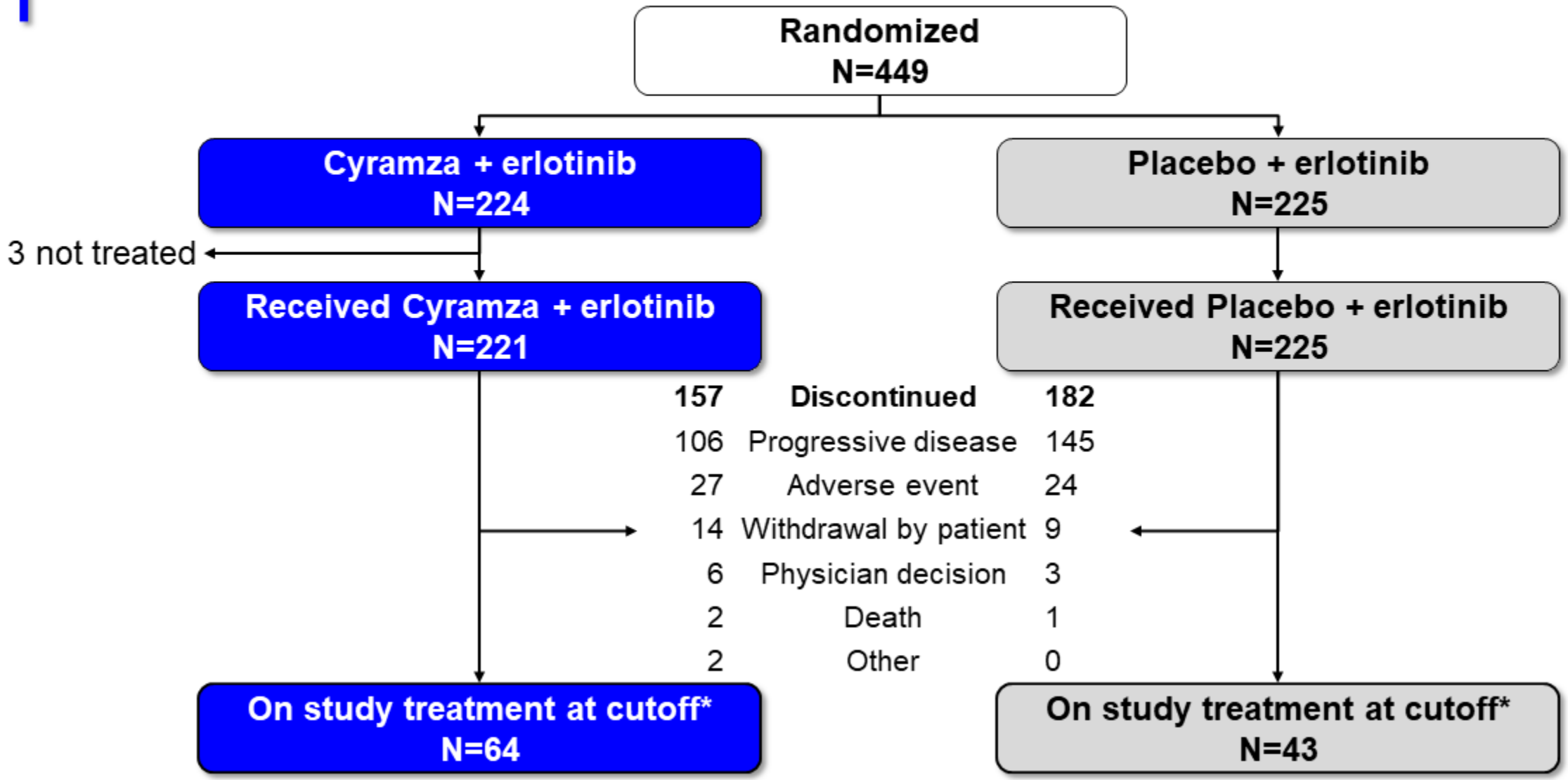
	Cyramza + Erlotinib (N=224)	Placebo + Erlotinib (N=225)
Sex		
Female	63%	63%
Age (years)		
Median (min-max)	65 (27-86)	64 (23-89)
Race		
Asian	77%	77%
Caucasian	23%	21%
Region		
East Asia	74%	76%
North America / Europe	26%	24%

RELAY: Disease Characteristics Similar Between Treatment Arms

	Cyramza + Erlotinib (N=224)	Placebo + Erlotinib (N=225)
Smoking history		
Never	60%	62%
ECOG performance status		
0	52%	53%
Disease stage at diagnosis		
Primary metastatic	87%	84%
EGFR mutation type[a]		
Exon 19 deletion	55%	53%
Exon 21 (L858R) mutation	44%	47%
EGFR testing method[a]		
therascreen / cobas	43%	45%
Other[b]	57%	55%

[a]Determined by local testing
[b]PCR and sequencing-based methods

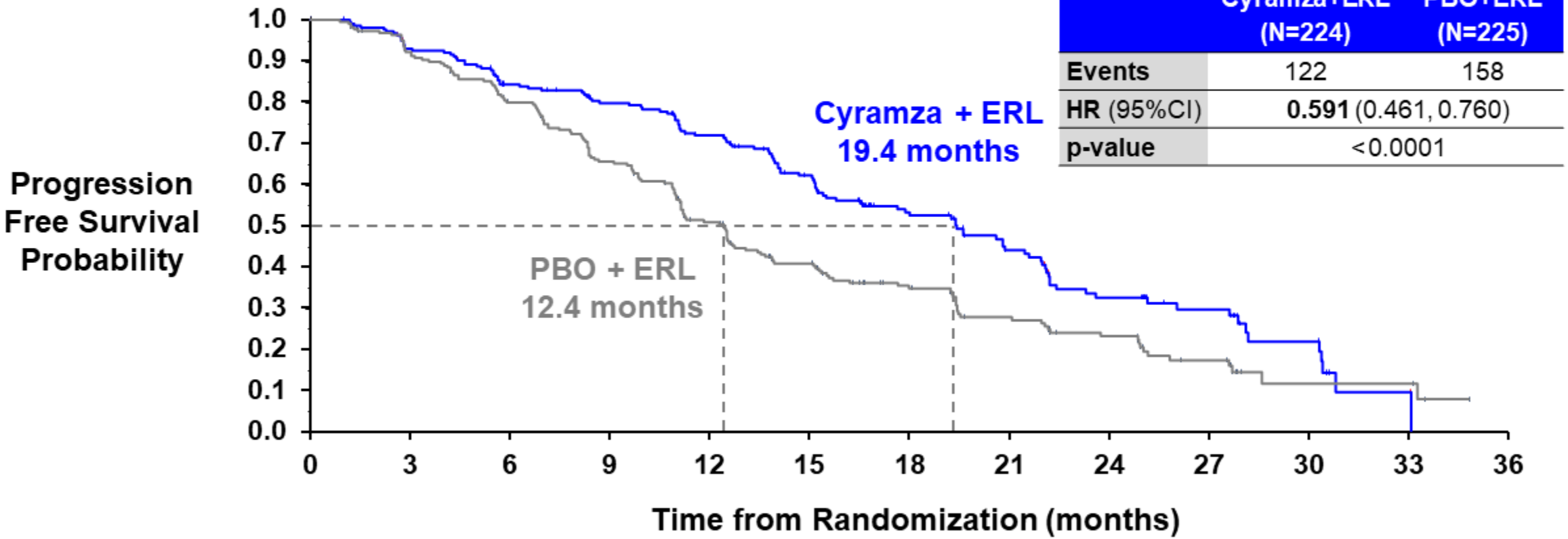
RELAY: Patient Disposition



*Data cutoff January 2019

RELAY: Cyramza Met Primary Efficacy Endpoint – Provided 7-Month Improvement in mPFS

	Cyramza+ERL (N=224)	PBO+ERL (N=225)
Events	122	158
HR (95%CI)	**0.591** (0.461, 0.760)	
p-value	<0.0001	

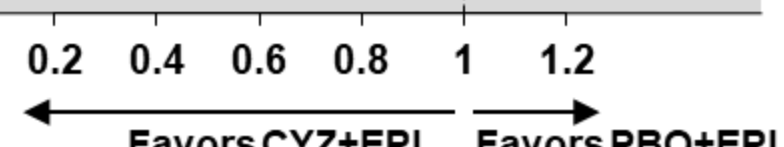


Patients at Risk

Cyramza + Erlotinib	224	196	170	154	133	103	69	49	32	20	10	1	0
Placebo + Erlotinib	225	196	167	136	99	72	52	37	27	15	4	4	0

Sensitivity Analyses Support Primary Results

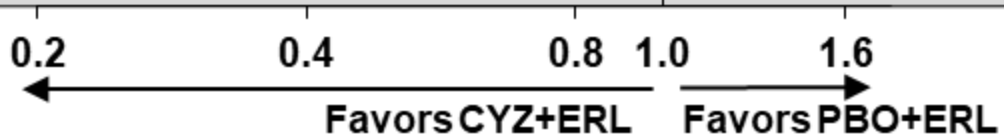
Analysis, n	CYZ	PBO	HR
Primary PFS analysis – 280 events	224	225	0.591
BIRC-assessment of PFS (stratified ITT population)	217	223	0.671
Per-protocol population analysis*	216	221	0.580
Using CRF strata[a]	224	225	0.607
Unstratified analysis	224	225	0.640
Treating lost to follow-up as progression*	224	225	0.591
Counting clinical and radiological progression as progression*	224	225	0.593
Ignoring missing tumor assessments*	224	225	0.597
Ignoring new anticancer treatment*	224	225	0.609
Ignoring anticancer therapy and missing tumor assessment*	224	225	0.615
Multivariate Cox regression analysis (adjusted for ECOG PS)	224	225	0.632



*Stratified by the Interactive Web Response System (IWRS)
a. stratified by sex, geographic region, EGFR mutation type, and EGFR testing method
BIRC = blinded independent radiological review committee

RELAY: Cyramza Provided PFS Benefit Consistently Across Subgroups

Subgroup, n	CYZ	PBO	HR
Overall	224	225	0.640
Male	83	83	0.505
Female	141	142	0.731
< 65 years	102	114	0.534
≥ 65 years	122	111	0.771
East Asia	166	170	0.636
North America / Europe	58	55	0.605
ECOG at baseline: 0	116	119	0.584
ECOG at baseline: 1	108	106	0.671
Smoking history: Ever	64	73	0.579
Smoking history: Never	134	139	0.694
Disease stage at diagnosis: IV	195	189	0.622
Disease stage at diagnosis: Other	29	34	0.735
Exon 19 deletion	123	120	0.651
Exon 21 mutation	99	105	0.618
therascreen / cobas	96	101	0.397
Other testing	128	124	0.873

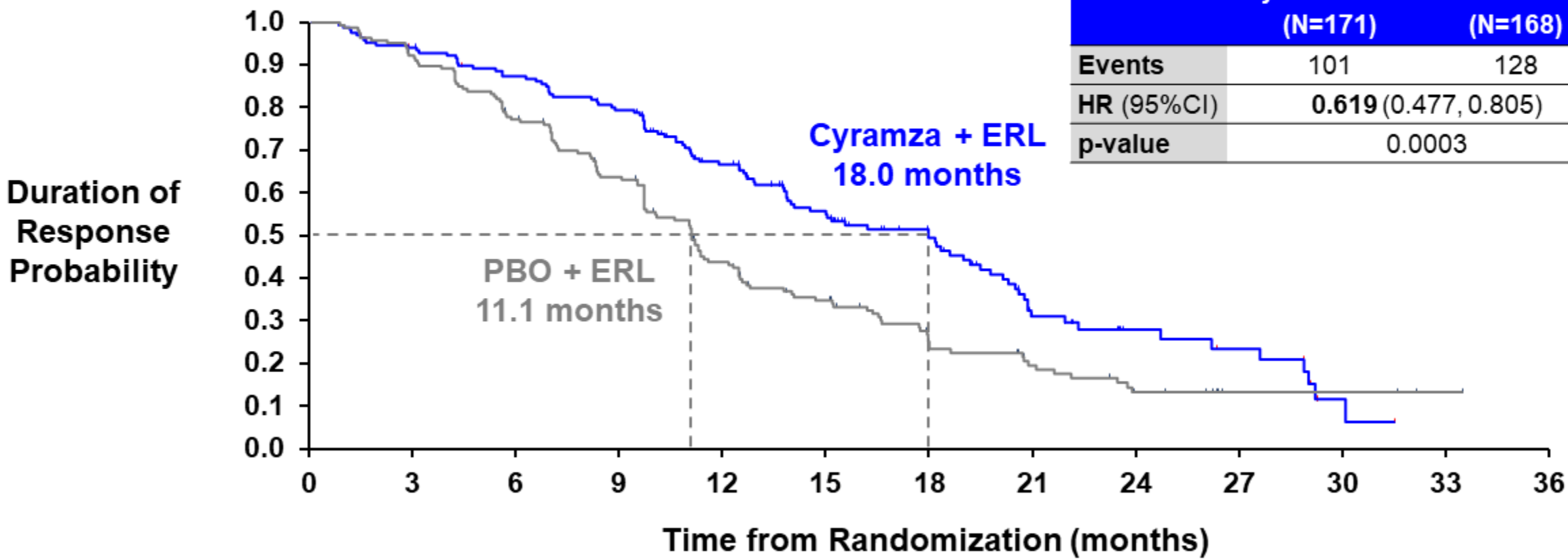


RELAY: Secondary Efficacy Results – Objective Response Rate and Disease Control Rate

Parameter	Cyramza + Erlotinib (N=224)	Placebo + Erlotinib (N=225)
ORR (CR+PR), % (95% CI)	**76.3%** (70.8, 81.9)	**74.7%** (69.0, 80.3)
p-value	**0.7413**	
DCR (CR+PR+SD), % (95% CI)	**95.1%** (92.3, 97.9)	**95.6%** (92.9, 98.2)
p-value	**1.000**	

RELAY: Secondary Efficacy Results – Duration of Response (DoR)

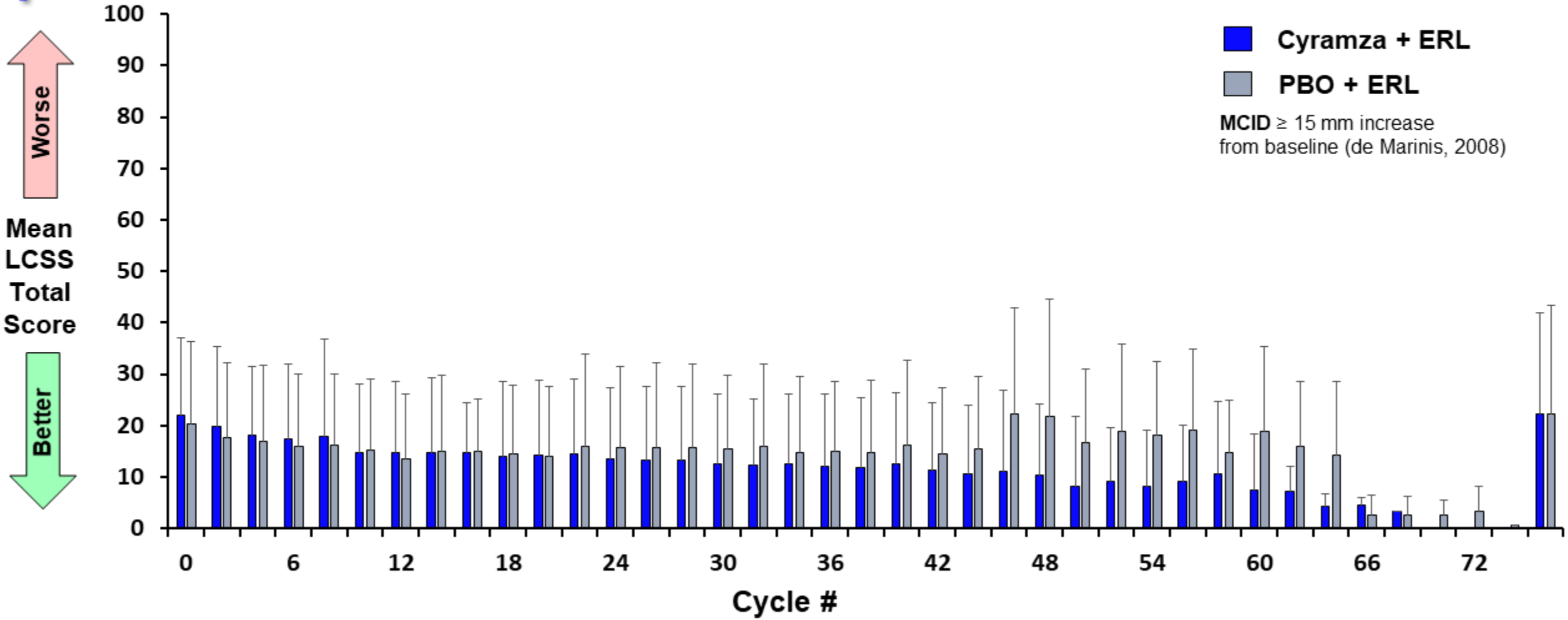
	Cyramza+ERL (N=171)	PBO+ERL (N=168)
Events	101	128
HR (95%CI)	**0.619** (0.477, 0.805)	
p-value	0.0003	



Patients at Risk

Cyramza + Erlotinib	171	155	142	128	99	68	48	21	12	9	2	0	0
Placebo + Erlotinib	168	152	127	101	65	47	28	19	10	3	3	1	0

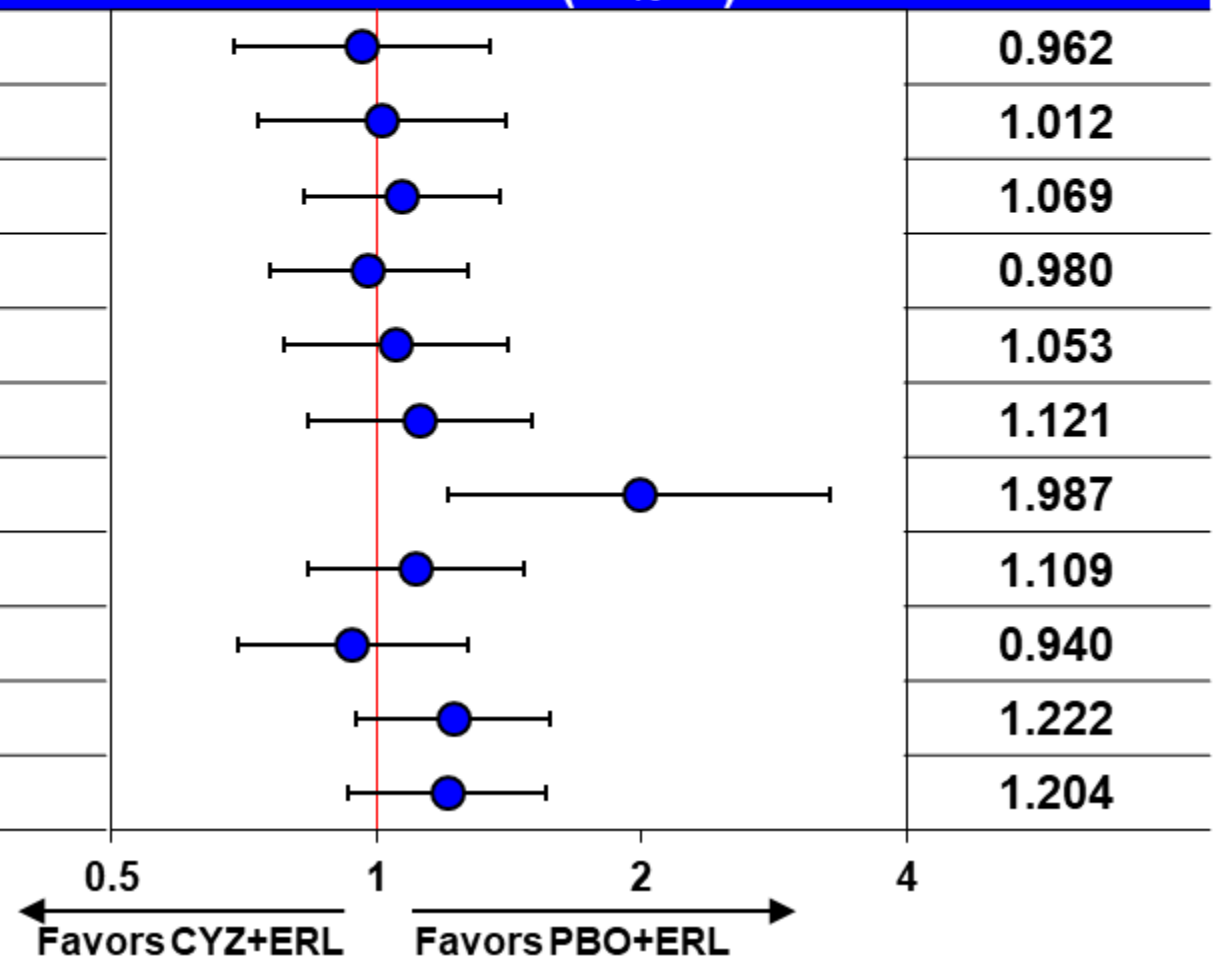
RELAY: Lung Cancer Symptom Scale (LCSS) Total Score Similar Between Arms, > 95% Patient Completion



Cycle	0	6	12	18	24	30	36	42	48	54	60	66	72	FU
N	432	388	332	282	239	174	127	91	66	42	23	5	3	260

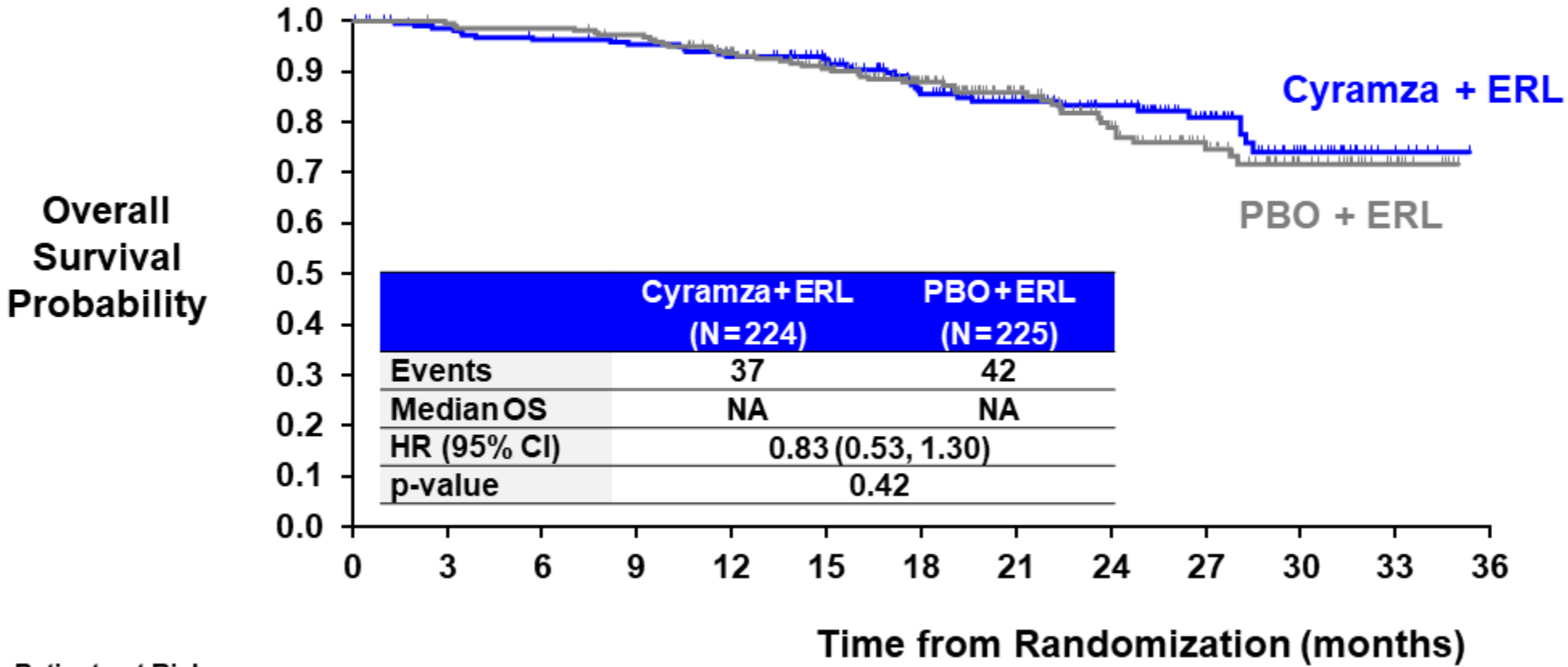
RELAY: Time to Deterioration for LCSS Components

Scale	Cyramza + ERL (N=224) # Events	Placebo + ERL (N=225) # Events	HR
Total LCSS	69	70	0.962
ASBI	75	72	1.012
Loss of appetite	121	119	1.069
Fatigue	113	116	0.980
Cough	92	86	1.053
Shortness of breath	95	88	1.121
Blood in sputum	47	23	1.987
Pain	102	94	1.109
Symptom distress	84	87	0.940
Activity level	126	112	1.222
Quality of life	125	107	1.204



ASBI = average symptom burden index

RELAY: Prespecified Interim OS

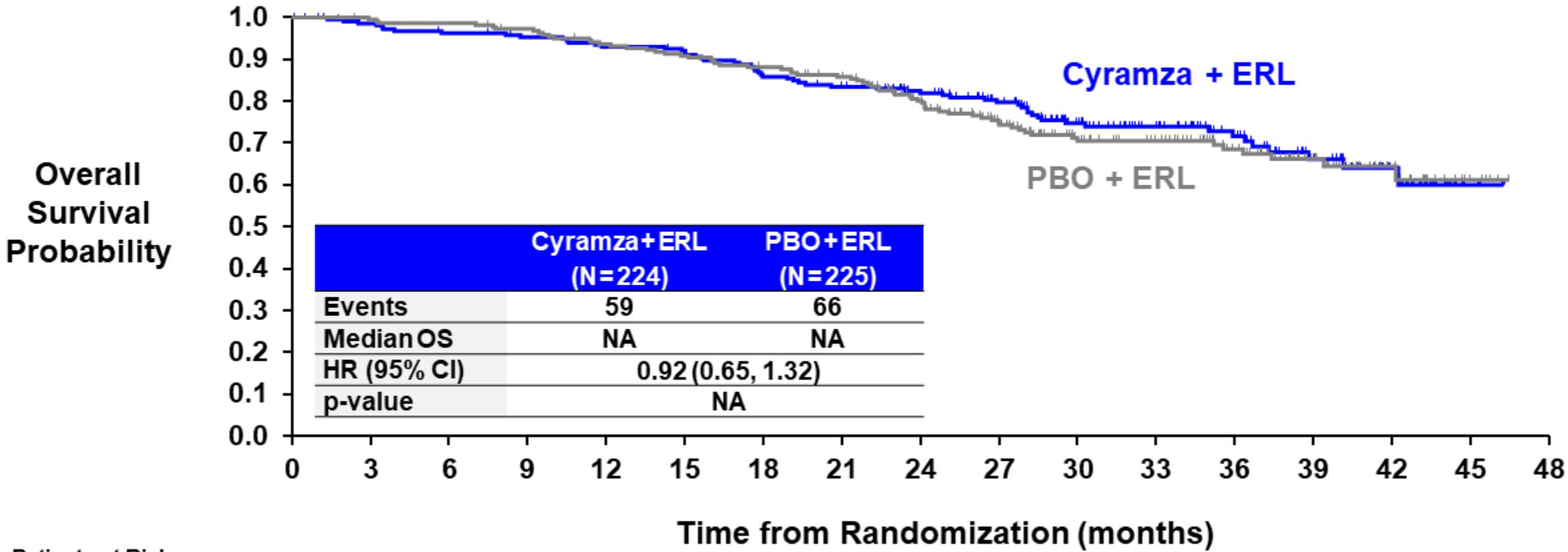


	Cyramza+ERL (N=224)	PBO+ERL (N=225)
Events	37	42
Median OS	NA	NA
HR (95% CI)	0.83 (0.53, 1.30)	
p-value	0.42	

Patients at Risk

Cyramza + Erlotinib	224	215	209	204	192	176	138	106	85	61	29	8	0
Placebo + Erlotinib	225	223	221	216	198	178	144	111	84	59	27	11	0

RELAY: OS Updated Per FDA Request



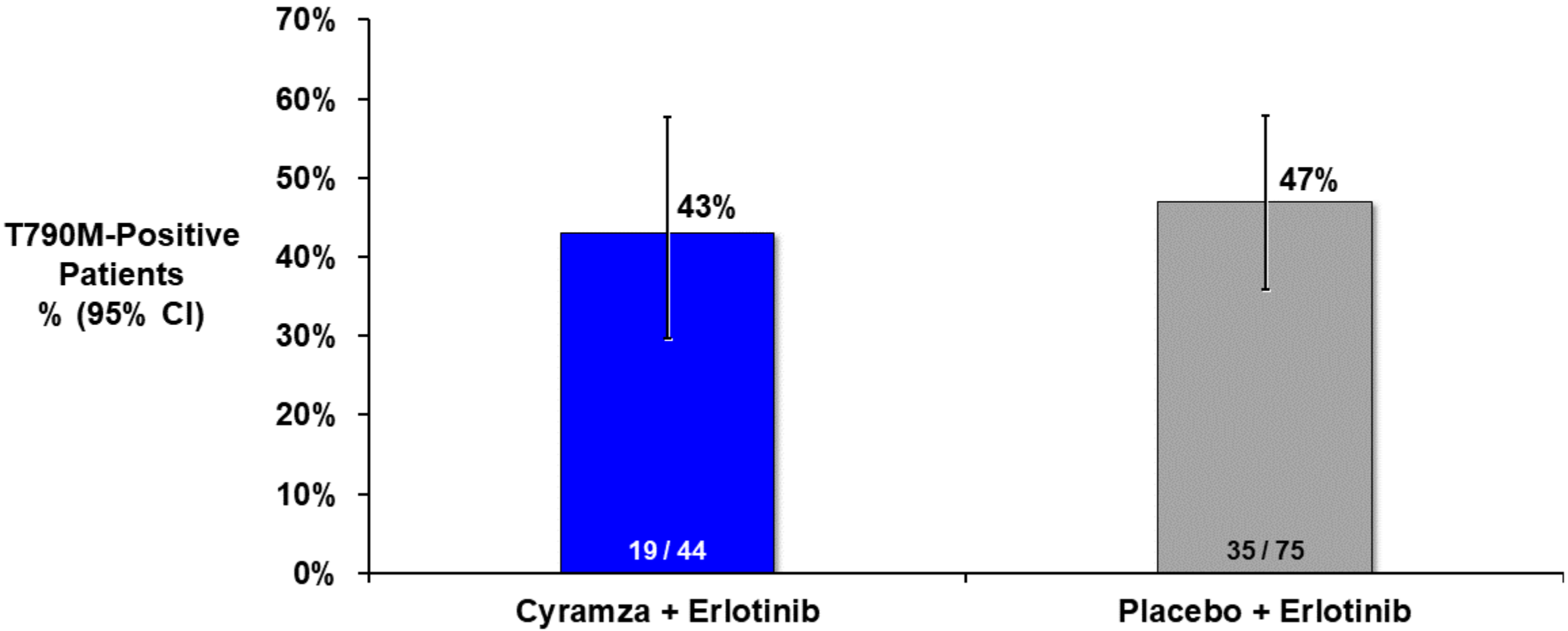
	Cyramza+ERL (N=224)	PBO+ERL (N=225)
Events	59	66
Median OS	NA	NA
HR (95% CI)	0.92 (0.65, 1.32)	
p-value	NA	

Patients at Risk

Cyramza + Erlotinib	224	215	209	205	200	197	181	174	161	138	104	84	61	39	16	2	0
Placebo + Erlotinib	225	223	221	216	207	201	194	186	163	134	104	89	65	40	21	6	0

Updated unplanned data cutoff 31 December 2019

RELAY: Post-Progression T790M Mutation Rates Similar Between Arms



Post-progression T790M mutation rate: Patients with post-progression 30-day follow-up next generation sequencing results where EGFR activating mutation detected

RELAY: Post-Discontinuation Anticancer Therapies (All Subsequent Lines)

Regimen	Cyramza + Erlotinib (N=224)	Placebo + Erlotinib (N=225)
Subsequent line of therapy, n/N (%) (excludes patients on study treatment)	120 / 157 (76%)	156 / 182 (86%)
EGFR TKI*	82%	79%
Erlotinib	52%	37%
Osimertinib	43%	39%
Chemotherapy	41%	51%
Immunotherapy	8%	13%
VEGF Antibodies	15%	24%
Bevacizumab	13%	21%
Cyramza	3%	6%

*TKIs included Gefitinib, Afatinib, Lazertinib, Nazeritinib, Erlotinib, Osimertinib
Patients could be included in multiple categories

RELAY: First Subsequent Post-Discontinuation Anticancer Therapies

Regimen	Cyramza + Erlotinib (N=224)	Placebo + Erlotinib (N=225)
First subsequent line of therapy, n/N (%)	120 / 157 (76%)	156 / 182 (86%)
EGFR TKI	89 / 120 (74%)	113 / 156 (72%)
Erlotinib	51%	35%
Osimertinib	15%	22%
Chemotherapy	23%	26%
Immunotherapy	3%	2%

- Post-hoc analysis: median time to chemotherapy or death of 33.7 months vs 29.4 months (HR 0.73; 95% CI 0.54, 1.0)

*TKIs included Gefitinib, Afatinib, Lazertinib, Nazeritinib, Erlotinib, Osimertinib

RELAY: Cyramza Demonstrates Statistically Significant, Clinically Meaningful and Durable Improvements

- PFS: median 7-month improvement
  - Treatment with Cyramza reduced hazard of disease progression or death by 41%
  - Consistent across sensitivity analyses and subgroups
- No evidence of detriment on overall survival
- Durable response 18.0 months vs 11.1 months
- Improved PFS2 (HR 0.69; 95% CI 0.49, 0.97)
- Delayed time to chemotherapy or death

RELAY Safety

Carla Visseren-Grul, MD

Global Medical Lead RELAY
Eli Lilly and Company

Safety Profile of Cyramza is Well-Established

- > 6,400 patients received Cyramza in clinical program
- > 125,000 patients treated worldwide across indications

RELAY: Exposure

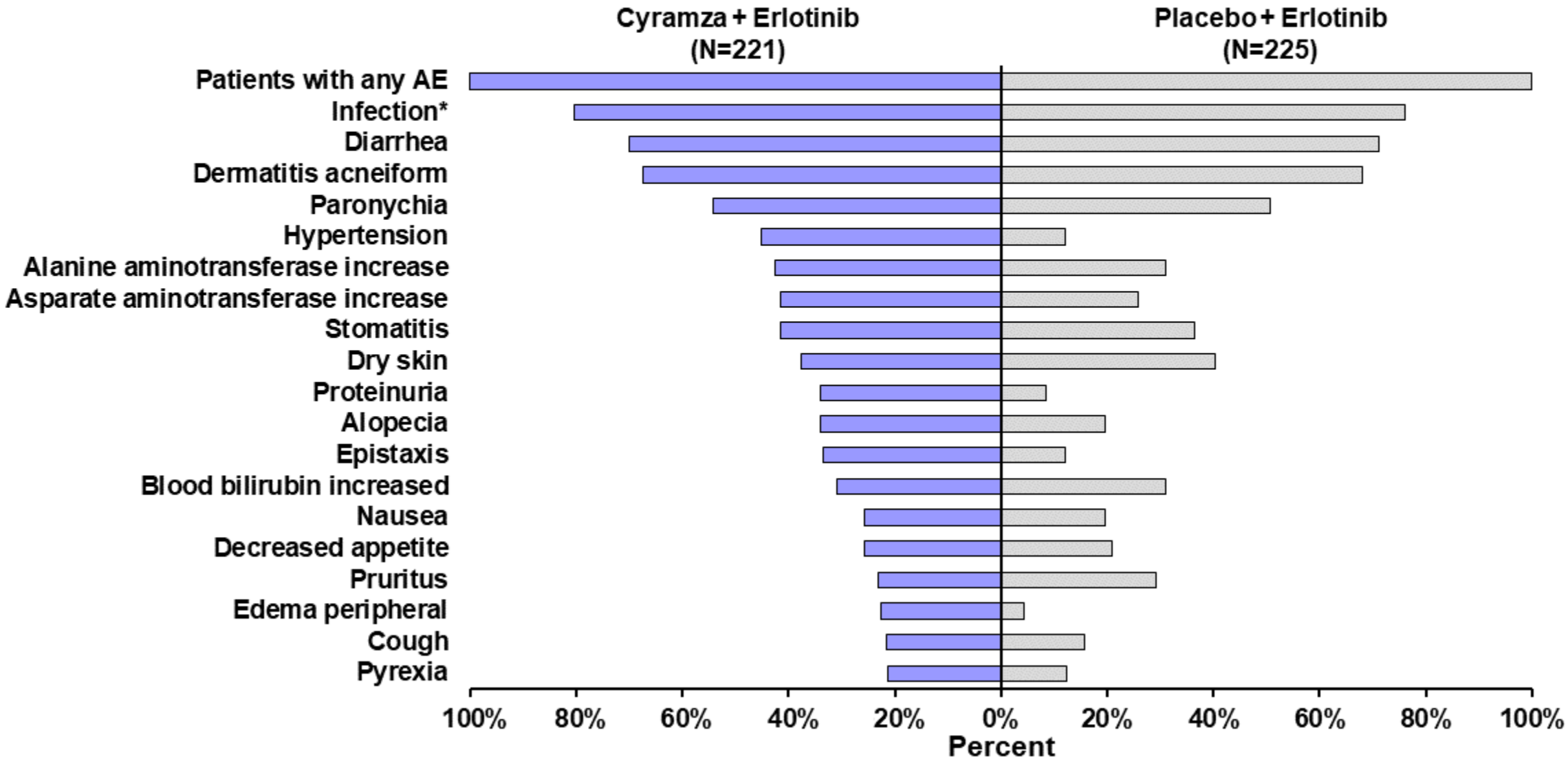
	Cyramza + Erlotinib (N=221)		Placebo + Erlotinib (N=225)	
	Cyramza	Erlotinib	Placebo	Erlotinib
Duration of therapy (months)				
Median (range)	**11.0** (0.5 – 33.8)	**14.1** (0.0 – 33.8)	**9.7** (0.5 – 35.4)	**11.2** (0.4 – 35.5)
Relative Dose Intensity (%)				
Median (range)	**94.5** (42.9 – 112.1)	**92.3** (30.2 – 100)	**97.7** (54.2 – 106.7)	**96.3** (27.9 – 100)
Infusions received per patients				
Median (range)	**21.0** (1.0 – 69.0)	**NA**	**19.0** (1.0 – 74.0)	**NA**

RELAY: Safety Overview

Patients with ≥ 1	Cyramza + Erlotinib (N=221)	Placebo + Erlotinib (N=225)
Treatment Emergent Adverse Event (TEAE)	100%	100%
AE Grade ≥ 3	72%	54%
Serious Adverse Event (SAE)	29%	21%
Patients who discontinued all study treatment due to AE	13%	11%
Death due to AE*	6 (3%)	0

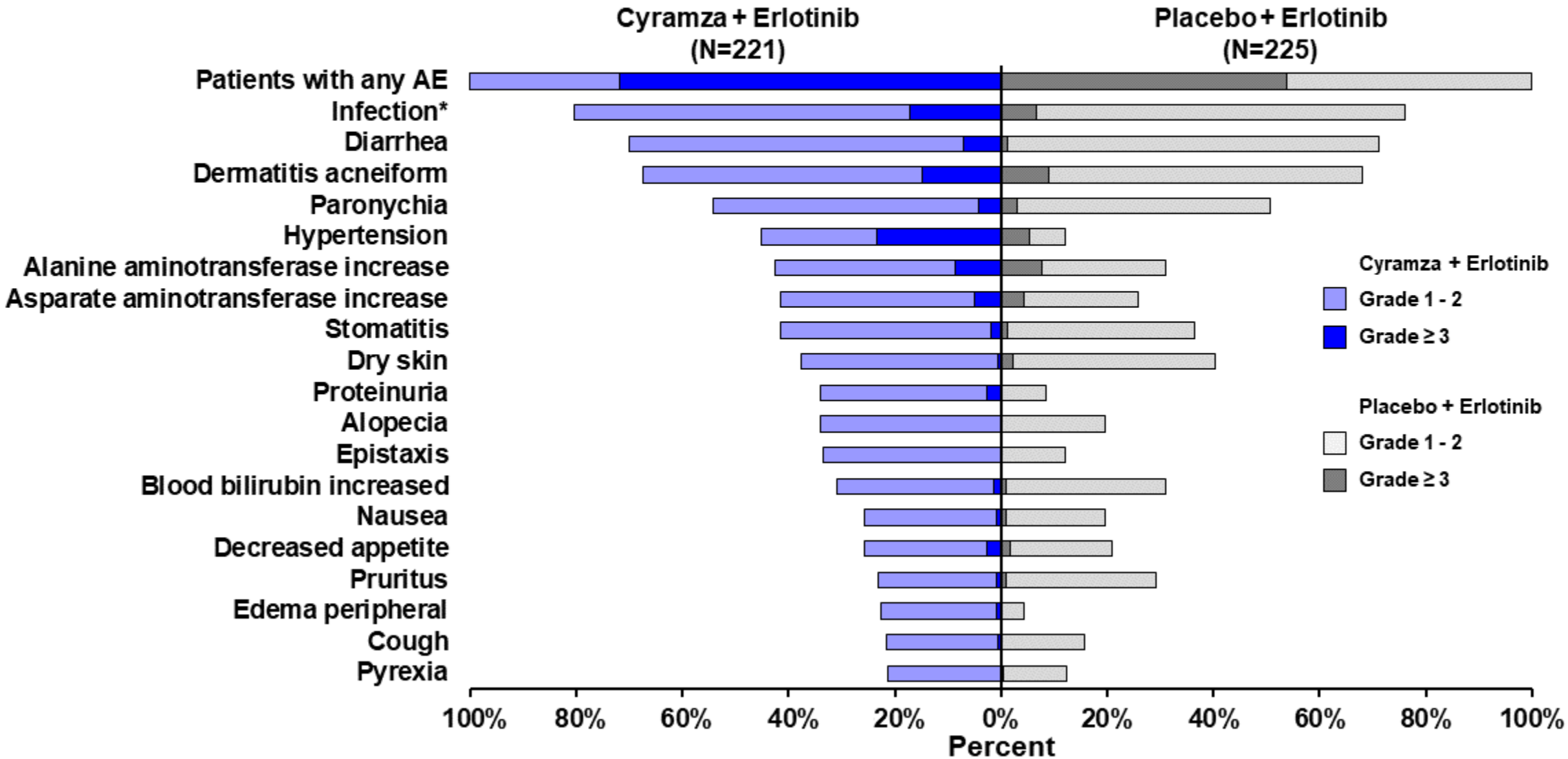
*Death due to AE on therapy or within 30 days of discontinuation

RELAY: Most Commonly Reported Any Grade AEs Occurring in ≥ 20% of Patients in Cyramza + Erlotinib Arm



*Composite term

RELAY: Most Commonly Reported AEs Occurring in ≥ 20% of Patients in Cyramza + Erlotinib Arm



*Composite term

RELAY: SAEs Reported (≥ 2 Patients in Cyramza + Erlotinib Arm)

MedDRA Preferred Term, %	Cyramza + Erlotinib (N=221)	Placebo + Erlotinib (N=225)
Patients with ≥ 1 SAE	29%	21%
Pneumonia	3%	< 1%
Cellulitis	2%	0
Pneumothorax	2%	1%
Decreased appetite	1%	0
Diarrhea	1%	< 1%
Hepatic function abnormal	1%	< 1%
Pyrexia	1%	2%
Alanine aminotransferase increased	< 1%	< 1%
Dyspnea	< 1%	< 1%
Hypertension	< 1%	0
Hypotension	< 1%	0
Pulmonary embolism	< 1%	< 1%
Skin infection	< 1%	0
Small intestinal hemorrhage	< 1%	0
Urinary tract infection	< 1%	0
Vomiting	< 1%	< 1%

RELAY: Deaths on Therapy or Within 30 Days of Treatment Discontinuation

	Cyramza + Erlotinib (N=221)	Placebo + Erlotinib (N=225)
On therapy or within 30 days of treatment discontinuation	8 (4%)	2 (0.9%)
Due to study disease	2 (0.9%)	2 (0.9%)
Due to AEs	6 (3%)	0

- No additional deaths due to AEs reported as of December 2019

RELAY: Deaths Due to AEs on Therapy or Within 30 Days of Treatment Discontinuation

AE	Therapy at Time of AE	Event Details
Hemothorax*	CYR, ERL	▪ Event start: Day 74 (28 days after last dose of CYR) ▪ Event started 5 days following thoracic drainage for pleural empyema
Encephalitis influenza	CYR, ERL	▪ Event start: Day 9 (9 days after 1 dose of CYR) ▪ Confirmed on microbiological testing
Lymphoma	CYR, ERL	▪ Event start: Day 80 of treatment ▪ Non-biopsy proven: small intestinal lymphoma following abdominal CT scan for melena ▪ Discontinued all study treatments due to progressive lung cancer Day 92, died Day 97
Renal failure	ERL	▪ Event start: Day 846 (202 days after last dose of CYR) ▪ Medical htx: bilateral hydronephrosis
Pneumonia	ERL	▪ Event start: Day 483 (454 days after last dose of CYR) ▪ Medical htx: ex-smoker and VATS partial lung resection
Pneumonia bacterial	ERL	▪ Event start: Day 318 (141 days after last dose of CYR; 5 days after last dose of ERL) ▪ Medical htx: ex-smoker, COPD, recurrent pneumothorax, bulla ligation, lung infections

*Investigator assessed as related to Cyramza, others not considered related to either study drug

RELAY: AEs Leading to All Study Treatment Discontinuation in ≥ 2 Patients

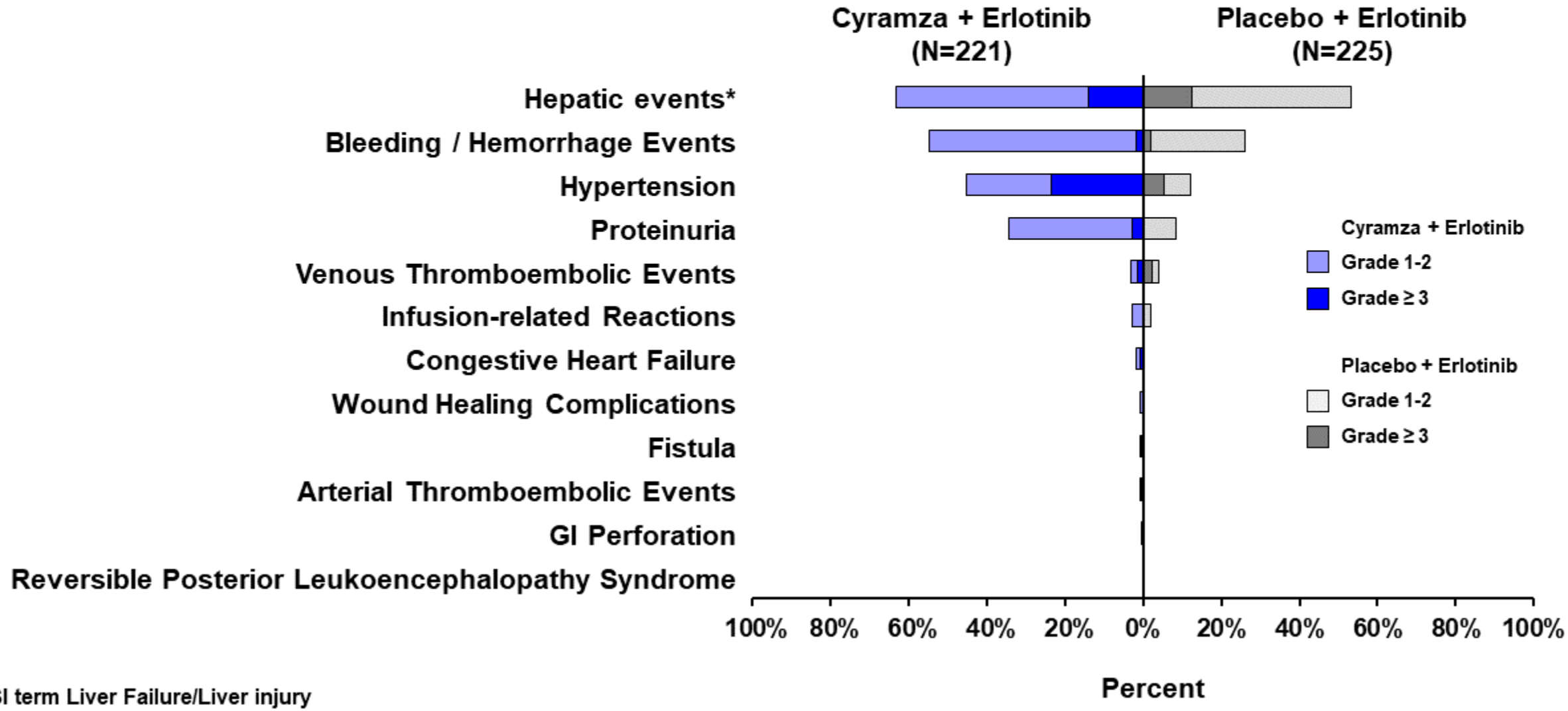
MedDRA Preferred Term	Cyramza + Erlotinib (N=221)	Placebo + Erlotinib (N=225)
Patients discontinued all study treatment due to AE	13%	11%
Alanine aminotransferase increased	1%	2%
Paronychia	1%	0
Dermatitis acneiform	< 1%	0
Proteinuria	< 1%	0

RELAY: AEs Leading to Discontinuation of Cyramza or Placebo in ≥ 2 Patients in Cyramza + Erlotinib Arm

MedDRA Preferred Term	Cyramza + Erlotinib (N=221)	Placebo + Erlotinib (N=225)
Patients with AE	33%	15%
Proteinuria	9%	0
Hyperbilirubinemia	6%	7%
Platelet count decreased	3%	< 1%
Neutropenia	3%	< 1%
ALT increased	1%	< 1%
Anemia	< 1%	0
Cardiac failure	< 1%	0
Hypoalbuminemia	< 1%	0
Weight decreased	< 1%	0

Adverse Events of Special Interest (AESI)

RELAY: Majority of AESIs Grade 1-2 and Manageable



*AESI term Liver Failure/Liver injury

Hypertension Known and Manageable Risk

- Managed with antihypertensive therapy and dose adjustments
- Of those with hypertension (n=100)
  - No Grade 4 or 5 events, 2 SAEs
  - 87% experienced single event with no treatment change
  - Cyramza dose adjustment: 13%
    - Dose delay: 12%
    - Dose omission: 1%
  - No patient discontinued all study treatment, 1 patient discontinued Cyramza alone

Bleeding / Hemorrhage Tolerable and Manageable

- Managed with dose adjustments and pharmacologic therapy
- Of those with bleeding / hemorrhage (n=121)
  - 7 SAEs
  - 90% required no treatment change
  - Cyramza dose adjustment: 9%
    - Dose delay: 5%
    - Dose omission: 3%
  - 1 patient had a blood transfusion
  - 1 patient discontinued all study treatment, 4 patients discontinued Cyramza alone

Proteinuria Managed through Dose Adjustments

- Of those with proteinuria (n=76)
  - 1 SAE
  - 62% did not require treatment change
  - Cyramza dose adjustments
    - Dose delay: 21%
    - Dose reductions: 24%
    - Dose omission: 20%
  - 2 patients discontinued all study treatment, 19 patients discontinued Cyramza alone

Safety Conclusions: Safety Profile Well-Characterized and Consistent with Expectations

- Combination well-tolerated
  - Supported by longer duration of treatment in Cyramza arm
  - High median relative dose intensities of each study drug
- Cyramza + erlotinib resulted in greater toxicity vs erlotinib alone
  - Detectable through routine monitoring
  - AEs managed through dose adjustments and supportive care

Clinical Perspective

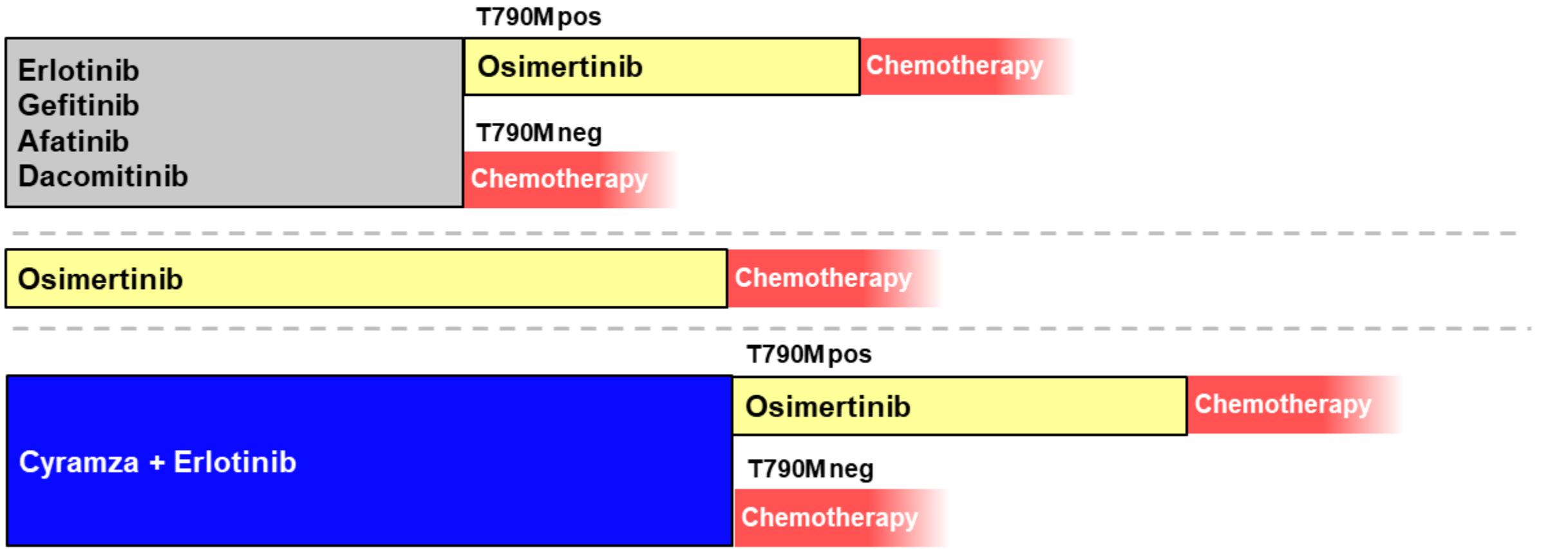
John Heymach, MD, PhD

Chair, Department of Thoracic Head and Neck Medical Oncology
M.D. Anderson Cancer Center
David Bruton, Jr. Chair in Cancer Research

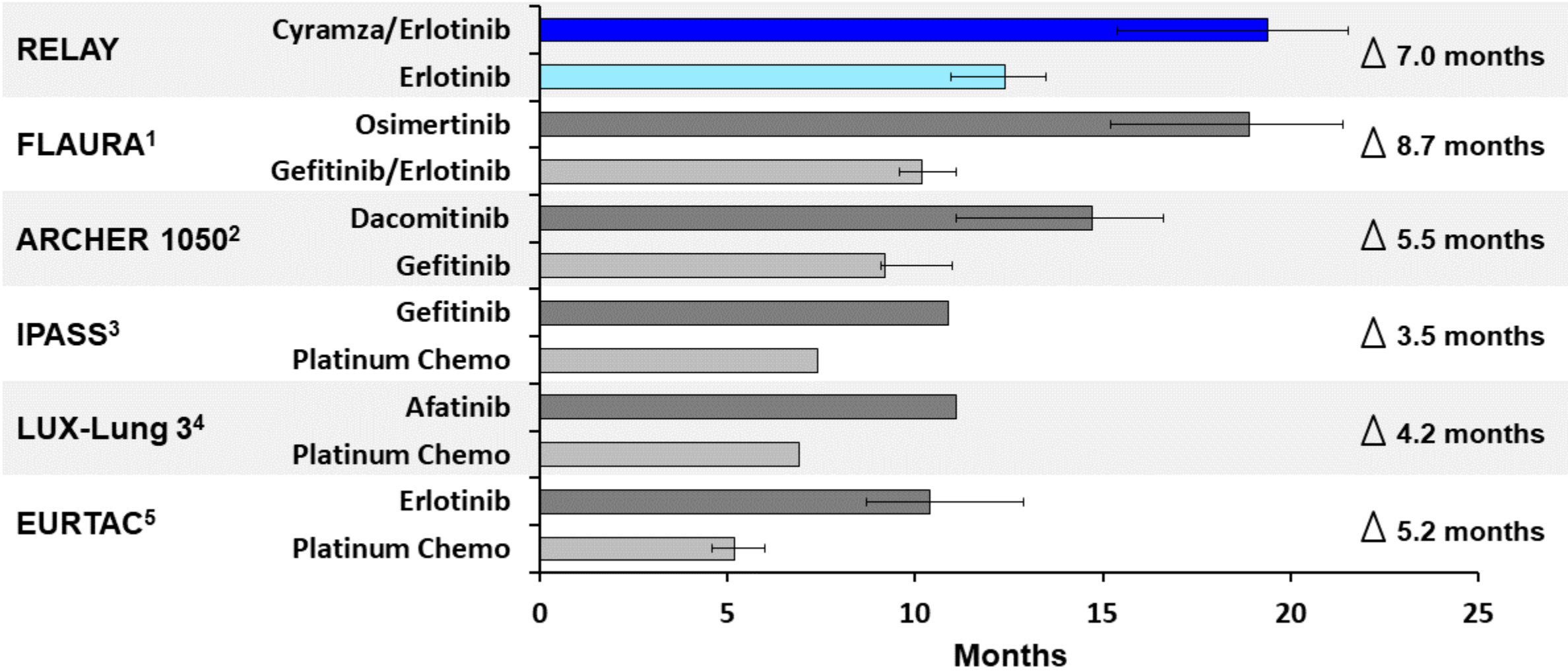
Cyramza + Erlotinib Combination Fills an Unmet Need for Patients with EGFR-Mutated NSCLC

- Combination expands first-line options for patients
- Viable options important to medical community
  - NCCN guidelines now recommend Cyramza + erlotinib
  - EMA approval
- Enables patients to receive osimertinib as 2nd line therapy
- May delay time to chemotherapy-based regimens

Cyramza + Erlotinib Would Add a New Treatment Strategy in EGFR-Mutant NSCLC to Support Unmet Need



Cyramza + Erlotinib Magnitude of Effect in PFS Amongst Largest Seen for NSCLC with Activating EGFR Mutations



1. Soria, 2018; 2. Wu, 2017; 3. Mitsudomi, 2010; 4. Sequist, 2013; 5. Rosell, 2012.

Cyramza + Erlotinib Demonstrated Efficacy by Multiple Clinically Meaningful Endpoints

- Combination demonstrated statistically significant and clinically meaningful improvements in PFS
  - Cyramza + ERL = 19.4 months
  - Placebo + ERL = 12.4 months

  } **7-month treatment difference**

- Additional support of meaningful improvement
  - DoR: HR=0.619 (0.477, 0.805)
- No detriment observed in overall survival analyses
- RELAY study well-conducted, accomplished its objectives

Safety Profile as Expected and Manageable

- Consistent with known safety profiles of individual treatment components and underlying disease
- Cyramza + erlotinib resulted in more toxicity vs erlotinib alone
  - AEs managed with dose adjustments and supportive care
- Patients able to receive subsequent therapy post progression

Cyramza + Erlotinib Demonstrated a Positive Benefit-Risk Profile

- Strong scientific rationale for combination of VEGFR-2 and EGFR inhibitors
- Combination demonstrated statistically significant and clinically meaningful improvement in PFS
- Safety profile as expected, understood and manageable
- Expands first-line options and enables use of EGFR TKIs as second-line therapy
  - Potentially delaying time to chemotherapy-based regimens

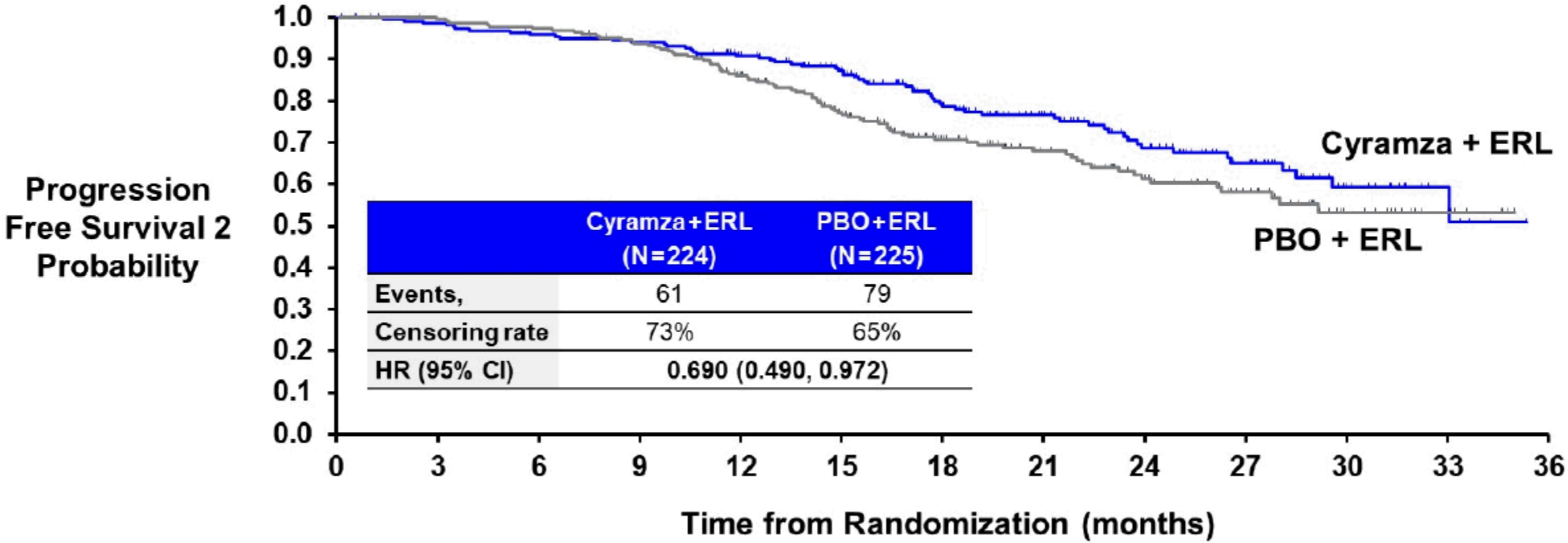
Cyramza (*ramucirumab*)

February 26, 2020

Oncologic Drug Advisory Committee
Eli Lilly and Company

Back-up Slides Shown on Screen

Lilly Briefing Book Figure 19: RELAY Kaplan-Meier Curves of Progression-Free Survival 2 (ITT Population)

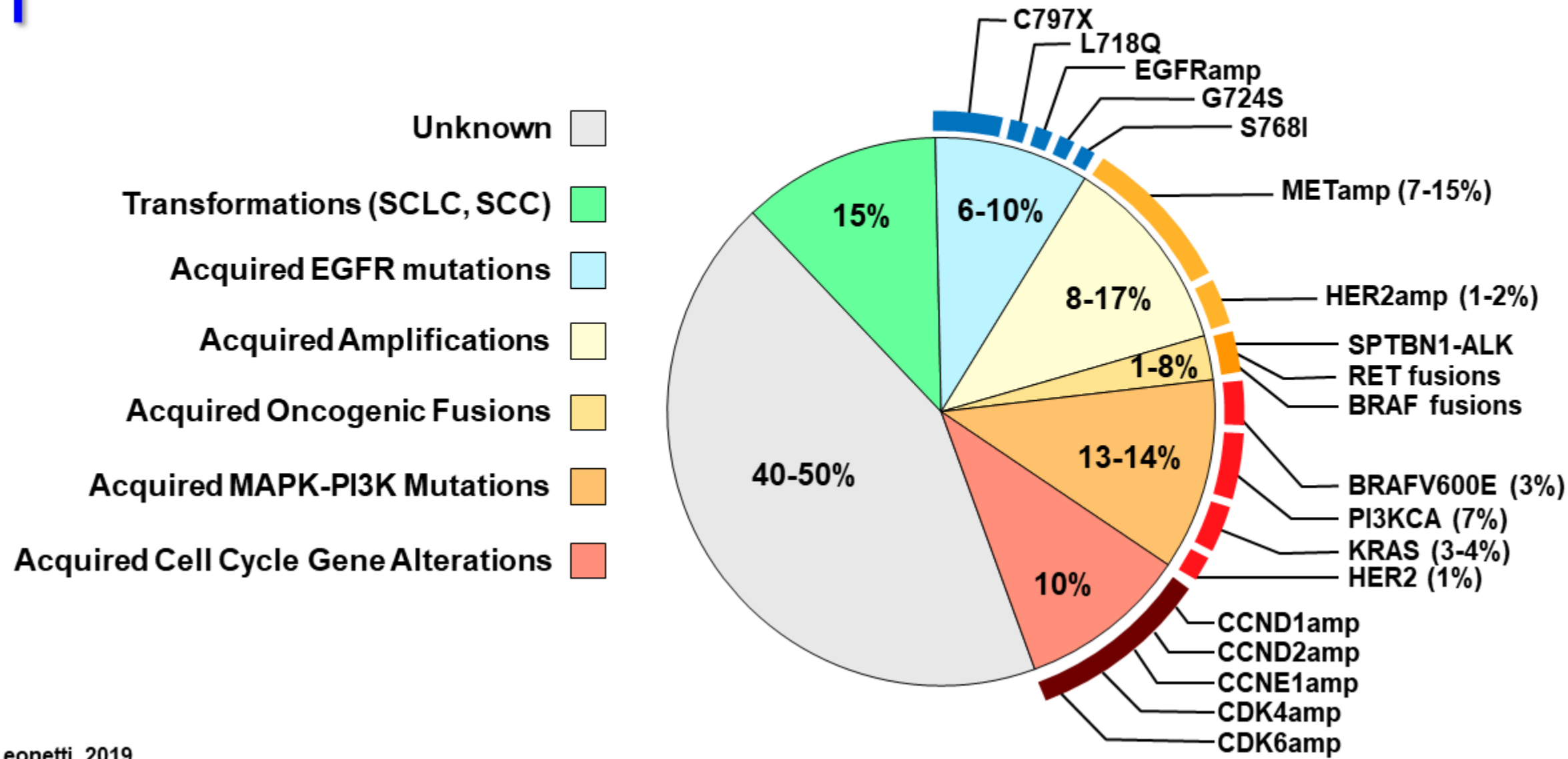


	Cyramza+ERL (N=224)	PBO+ERL (N=225)
Events,	61	79
Censoring rate	73%	65%
HR (95% CI)	0.690 (0.490, 0.972)	

Patients at Risk

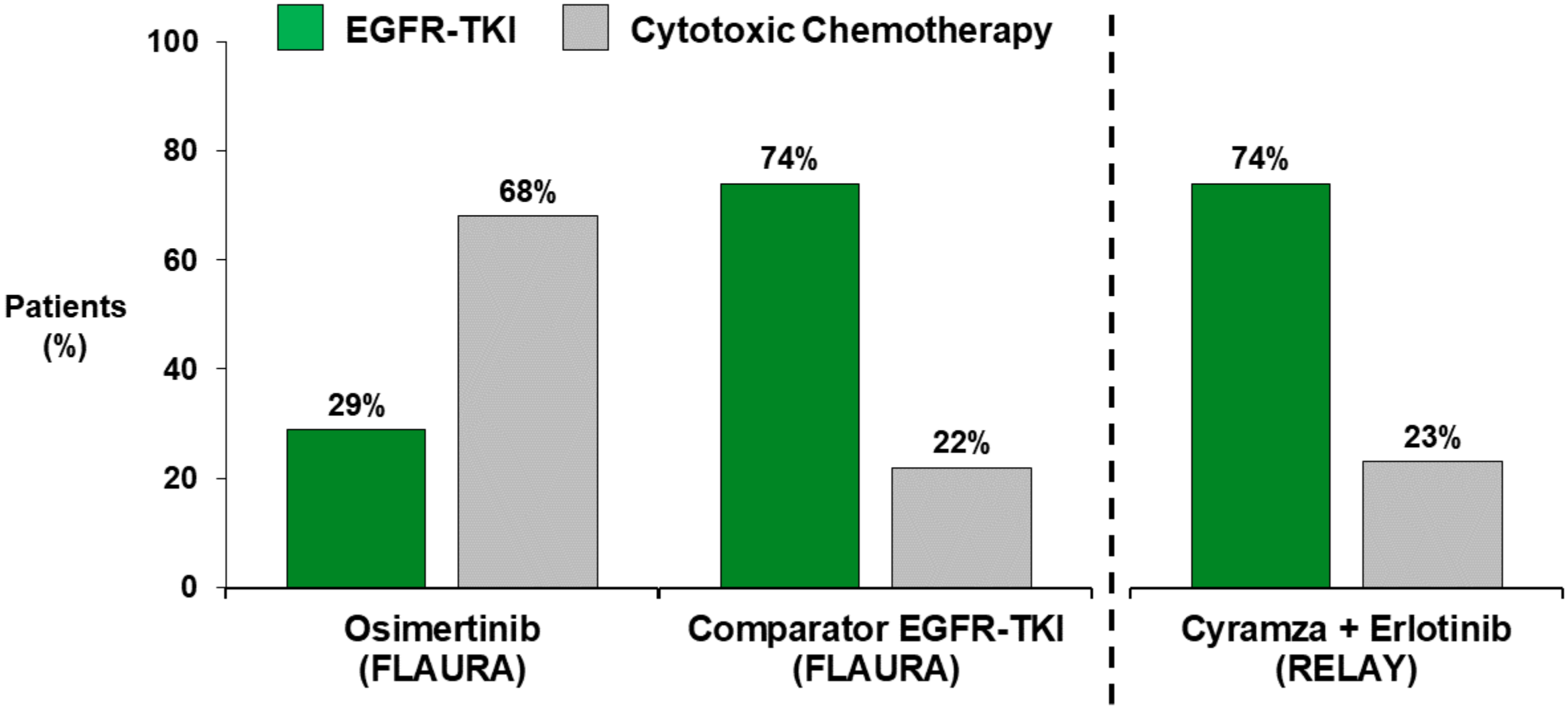
Cyramza + Erlotinib	224	215	208	201	187	165	126	97	71	50	21	7	0
Placebo + Erlotinib	225	223	218	208	181	149	115	89	66	45	17	8	0

Resistance to Osimertinib Largely EGFR-Independent: No Targeted Agents Once Patient Progresses

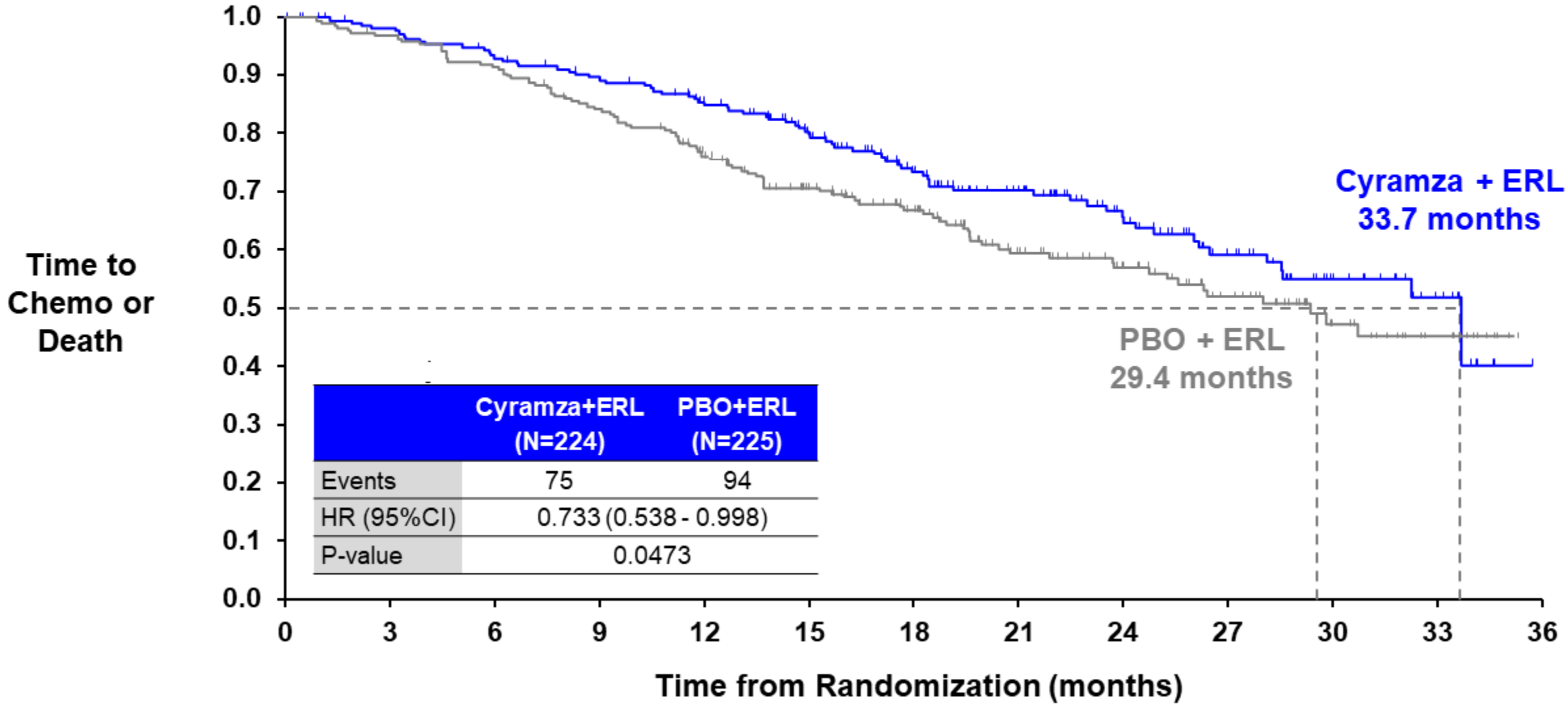


Leonetti, 2019

First Subsequent Therapies Received (FLAURA vs RELAY)

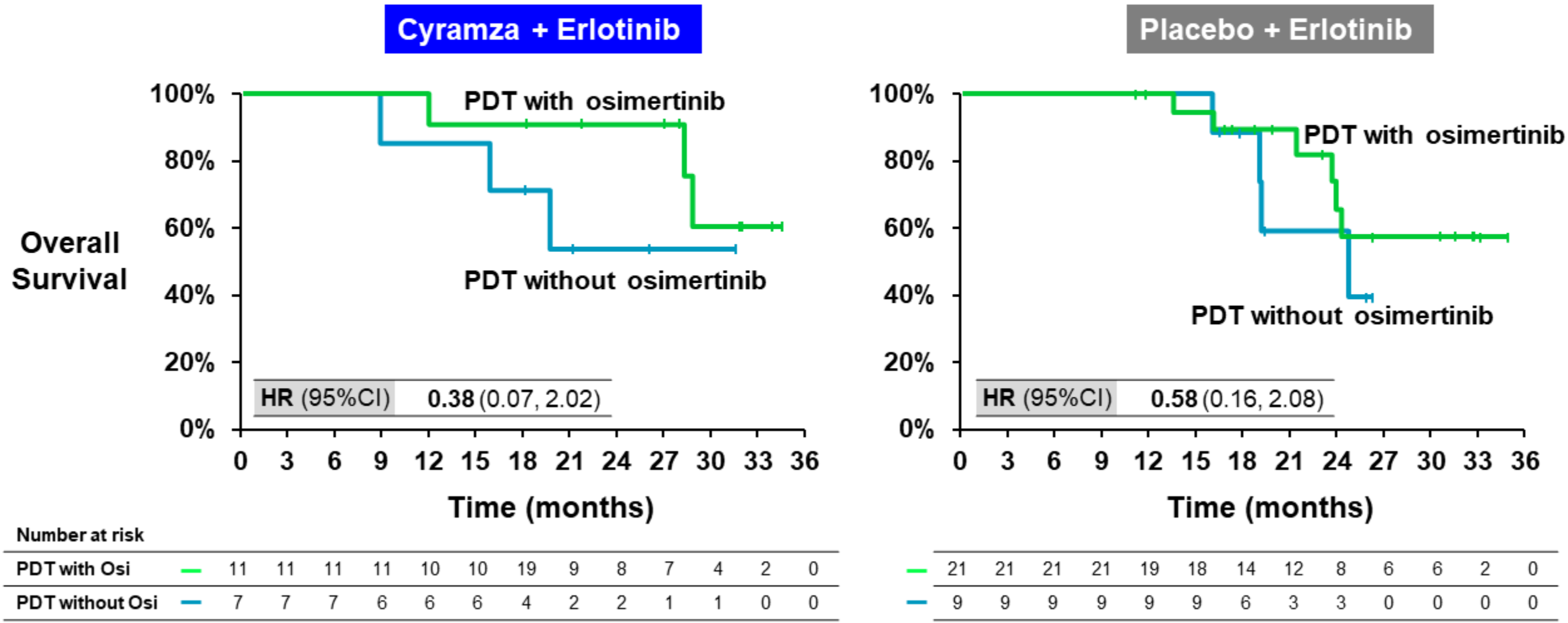


RELAY: Time to Chemotherapy or Death



	Cyramza+ERL (N=224)	PBO+ERL (N=225)
Events	75	94
HR (95%CI)	0.733 (0.538 - 0.998)	
P-value	0.0473	

Overall Survival for Osimertinib as PDT in Patients who Acquired T790M on RELAY Regimen



RELAY: HR Projections at Final OS Analysis at 300 Events (Based on 31 December 2019 Data Cut)

Probability HR point estimate less than indicated values		Probability 95% upper confidence limit less than indicated values	
HR Point Estimate	Probability	Estimated 95% Upper Limit	Probability
< 0.9	0.69	< 0.9	0.27
< 1.0	0.84	< 1.0	0.46
< 1.1	0.93	< 1.1	0.64
< 1.2	0.97	< 1.2	0.78
< 1.3	0.99	< 1.3	0.88

RELAY: Challenges with Powering for OS

Given current RELAY outcomes (PFS difference and anticipated median OS):

- Assuming 7-month mPFS difference translates to OS
  - ↳ Implied OS medians would be ~50 vs 57 months
    - ↳ Resulting OS HR assumption would be 0.88

- A study with 80% power assuming an HR=0.88 would require
  - 2740 patients
  - Potentially 8-10 years to complete

RELAY: AE Overview – Age Subgroups (≥ 65 Years vs < 65 years)

Patients with ≥ 1	Cyramza + Erlotinib		Placebo + Erlotinib	
	Age ≥ 65 (N=119)	Age < 65 (N=102)	Age ≥ 65 (N=111)	Age < 65 (N=114)
Treatment Emergent Adverse Event (TEAE)	100%	100%	100%	100%
Grade ≥ 3 TEAE	76%	68%	60%	47%
Serious Adverse Event (SAE)	35%	23%	26%	16%
Patients who discontinued all study treatment due to AE	13%	14%	15%	6%
Death due to AEs on study treatment*	3 (2.5%)	3 (2.9%)	0	0

*Death due to AE combine to show during treatment and within 30 days of discontinuation

RELAY: AE Overview – Age Subgroups (≥ 70 Years vs < 70 Years)

Patients with ≥ 1	Cyramza + Erlotinib		Placebo + Erlotinib	
	Age ≥ 70 (N=64)	Age < 70 (N=157)	Age ≥ 70 (N=59)	Age < 70 (N=166)
Treatment Emergent Adverse Event (TEAE)	100%	100%	100%	100%
Grade ≥ 3 TEAE	81%	68%	56%	53%
Serious Adverse Event (SAE)	41%	25%	27%	19%
Patients who discontinued all study treatment due to AE	16%	12%	12%	10%
Death due to AEs on study treatment*	1 (2%)	5 (3%)	0	0

*Death due to AE combine to show during treatment and within 30 days of discontinuation

Overall Survival in T790M Negative Patients at Progression